Synthesis of Ethyl *trans*-Cinnamate via Wittig Reaction & Assessment of Stereoselectivity with 60 MHz ^{1}H NMR Spectroscopy

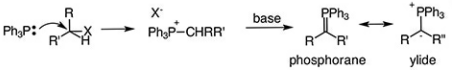
Introduction

The Wittig reaction is a high-yielding, versatile synthetic procedure used to construct carbon-carbon double bonds. Unlike other sp^2 bond forming reactions this provides convenient access to *cis* stereochemistry. At the time the reaction was discovered, *cis* stereochemistry was not reliably afforded by other synthetic means.

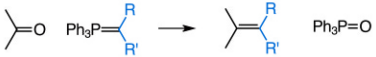
It won Georg Wittig the Nobel Prize in Chemistry in 1979.

The first step in the reaction is formation of a phosphorus ylide, known as the Wittig reagent. This occurs via:

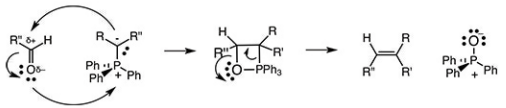
(1) a simple S_N2 reaction between triphenylphosphine and a primary or secondary alkyl halide;
(2) subsequent deprotonation of the resultant phosphonium salt with a suitable base.



This Wittig reagent, represented with either a phosphorane or zwitterion Lewis structure, is a source of negatively charged carbon (*i.e.*, a carbon nucleophile). This can react with positively charged carbon atoms such as those found in carbonyls of an aldehyde or ketone.



To account for the high stereoselectivity of this reaction the mechanism is proposed to proceed through a concerted [2+2] cycloaddition where a 4-membered oxaphosphetane intermediate is formed. This decomposes rapidly to afford two thermodynamically stable species: triphenylphosphine oxide and a carbon-carbon double bond.

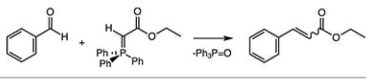


Procedure

While there are many synthetic procedures utilizing Wittig chemistry, we choose the following for its simplicity in generating ethyl cinnamate, a common spice flavour/fragrance molecule.[1] The procedure is solvent free, and the pre-prepared Wittig reagent doesn't require anhydrous conditions or caustic bases.

Weigh (carbethoxymethylene)triphenylphosphorane into a clean vial charged with a stir bar. Add benzaldehyde to the Wittig reagent and ensure that the reaction has been mixed rigorously prior to placing it on the stir plate. Stir the resultant slurry at room temp. for 10-15 minutes.

Add 2 mL of hexane to the resultant gel and stir well, scraping the sides of the vial. Filter the solution from the white solid. Evaporate off the hexane until only the liquid product remains. Weigh your product and determine the percent yield of the crude product.



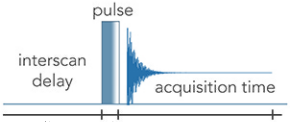
MW (g/mol):	106.12	348.37	176.21
ρ (g/mL):	1.045	-	1.05
ME:	1	1.05	1
Added:	50.8 mL	0.2 g	-
mmol:	0.5	0.5	0.5
Expected yield:	-	-	88 mg

NMR Data Acquisition

Prepare NMR samples to a total sample volume of ~0.5 mL in $CDCl_3$ or d_6-acetone:

(1) 100 mL Benzaldehyde
(2) 0.5 M Wittig Reagent
(3) 100 mL crude *trans*-ethyl cinnamate
(4) 20 mg of hexane-insoluble white precipitate

Acquire a 4 scan ^{1}H NMR for all four samples with the 1D experiment. This pulse sequence is shown below:



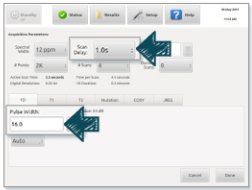
d1 = recycle delay that allows spins to fully relax between scans.
p1 = time pulse applied to tilt nuclear spins to 90°
at = time over which free induction decay (FID) is observed

d1 and p1 can be easily accessed from the NMReady interface by:

(1) Selecting orange 'Settings' button from the main screen

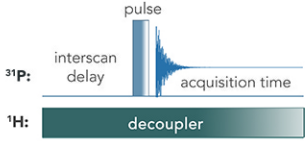
(2) changing 'Scan Delay' and 'Pulse Width', respectively.

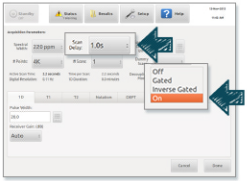
For a qualitative structural analysis, 0.5-1 sec scan delay is more sufficient with the default 90° pulse, but these can be modified as desired.



› ^{1}H NMR: 4 scans x 4.4 sec/scan **–** 18 sec/sample; 18 sec/sample x 4 samples **– *1.1 min/student***

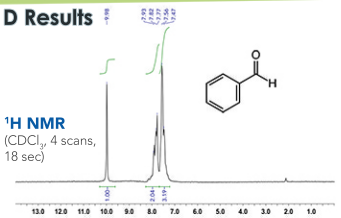
An optional 16 scan phosphorus decoupled (^{31}P{^{1}H}) spectrum can also be collected for the Wittig Reagent and hexane insoluble precipitate. This experiment includes the same basic 1D pulse on the ^{31}P channel while simultaneously applying a low power pulse train to the ^{1}H channel to average away ^{1}H-^{31}P couplings that complicated the ^{31}P spectrum & reduce its effective sensitivity.



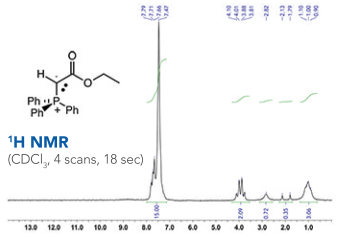


› ^{31}P{^{1}H} NMR: 16 scans x 4.2 sec/scan **–** 1.1 min/sample; 1.1 min/sample x 2 samples **– *2.2 min/student*** *(optional)*

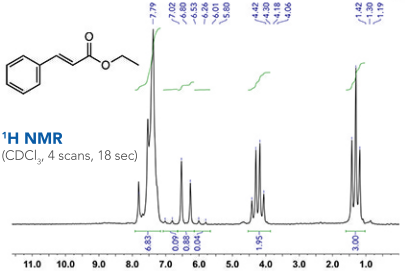
1D Results



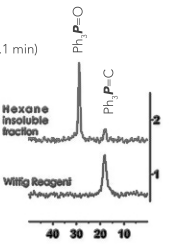
^{1}H NMR
($CDCl_3$, 4 scans, 18 sec)



^{1}H NMR
($CDCl_3$, 4 scans, 18 sec)



^{1}H NMR
($CDCl_3$, 4 scans, 18 sec)

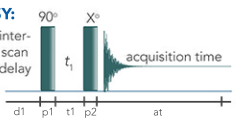


^{31}P{^{1}H} NMR
($CDCl_3$, 16 scans, 1.1 min)

2D NMR Data Acquisition

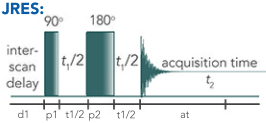
In the 1D spectrum of the conjugated alkene, it appears as though only one vinyl resonance is resolved (δ = 6.40 ppm); the second one overlaps with the aromatic multiplet (δ = 7.21-8.0ppm). These overlapping peaks can be resolved using 2D methods, such as H-H COrrelation SpectroscopY (COSY) and/or the J-RESolved (JRES) experiment. The pulse sequences & related NMReady settings are shown below:

COSY:

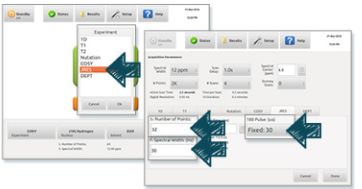


d1 = recycle delay
p1 = 90° pulse
t1 = delay between pulses
p2 = second pulse - typically 35° or 90°
at = time FID observed

JRES:



The COSY can be easily setup in the 'Settings' tabs by selecting:
(1) the number of t1 points (rows) *(shown at 64 here)*
(2) the f1 spectral width is the same as the f2 *(12 ppm here)*
(3) the default (auto) for a second 90° pulse

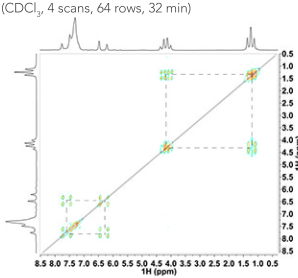


The JRES can be easily set up in the 'Settings' tab by selecting:
(1) the number of t1 points (rows) *(shown at 32 here)*
(2) the f1 spectral width with expected value *(30 Hz here)*
(3) the 180° pulse according to default (auto) or more precisely with a nutation experiment

2D Results

COSY

($CDCl_3$, 4 scans, 64 rows, 32 min)



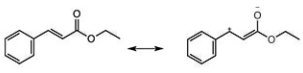
The COSY spectrum shows 2 isolated spin systems:

(1) the ethyl fragment

(2) the vinyl groups

The COSY spectrum clearly resolves the second vinyl doublet from beneath the phenyl resonances.

The large difference in chemical shift of the two the vinyl peaks can be explained using resonance structures.



JRES

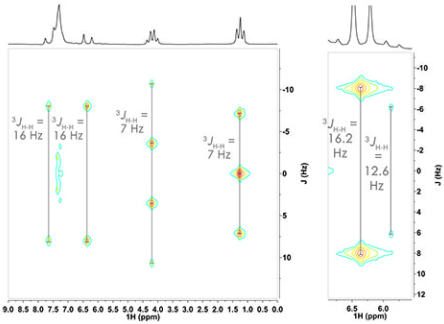
($CDCl_3$, 4 scans, 32 rows, 17 min)

Alternatively, a JRES can be used to resolve and assign the multiplicity of these peaks. This experiment decouples chemical shift from coupling constant.

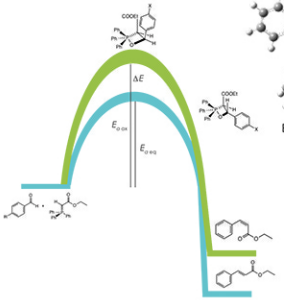
The doublets are clearly separated from the phenyl resonances and exhibit a $^3J_{H\text{-}H}$ = 16 Hz.

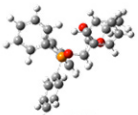
If we zoom in a little further, the JRES also confirms the presence of a second species ($^3J_{H\text{-}H}$ = 12.6 Hz), as was visible in the 1D ^{1}H NMR spectrum. The similarity in multiplicity, but differences in coupling constants suggest that perhaps we have evidence for the existence of two isomers.

Typical *trans* couplings are in the 12-24 Hz range, while *cis* couplings are smaller, and reside in the 6-12 Hz range.



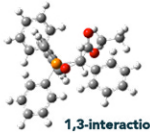
Gaussian Calculations





1,2-interactions

E_{ax} = -1688.3900 Hartrees



1,3-interactions

E_{eq} = -1688.3924 Hartrees

Gaussian calculations can also be correlated with this experiment to explain the observed ratio of *cis*- to *trans*- isomers. These density functional theory (DFT) calculations estimate the relative energy of the oxaphosphetane transition states,[2] depending whether or not the bulky aldehyde substituent is in the equatorial or axial position.

For the case of benzaldehyde, the optimized geometry found by the Becke 3-parameter Yee-Lang-Parr hybrid functional with a 6-31G** basis set (B3LYP/6-31G**) places the benzaldehyde in an equatorial position, as this is a 1,3- interaction as opposed to the axial case where the benzaldehyde substituent is eclipsed in a 1,2-orientation by the Wittig Reagent's ester group.

Gaussian Calculations cont.

The difference in energy between was found to give an calculated trans : cis ratio of 93.2 : 6.8. This is in agreement with other computational studies.[3]

$$\Delta E = -0.0024 \text{ Hartrees} = -6.336 \text{ kJ/mol}$$

$$ln\left(\frac{[cis]}{[trans]}\right) = -\frac{\Delta E}{RT}$$

$$\left(\frac{[cis]}{[trans]}\right) = e^{-\frac{6.336kJ/mol}{(8.3145J/molK)(293K)}}$$

$$\left(\frac{[cis]}{[trans]}\right) = \frac{[cis]}{100-[cis]} = 0.073777$$

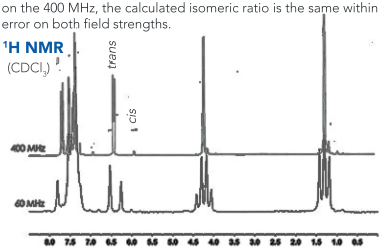
CALCULATED:

$$[cis] = 6.87$$

$$[trans] = 93.13$$

The calculations correlate well to the experimental data acquired on both the NMReady-60 and on a 400 MHz instrument. It is interesting to show that despite the greater peak dispersion on the 400 MHz, the calculated isomeric ratio is the same within error on both field strengths.

^{1}H NMR
($CDCl_3$):

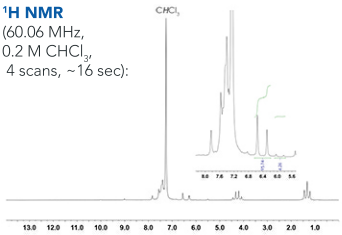


EXPERIMENTAL:

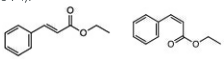
	60 MHz	400 MHz
(E)	95.56	95.54
(Z)	4.44	4.46

Proteo- vs. Deutero Solvents

^{1}H NMR
(60.06 MHz,
0.2 M $CHCl_3$,
4 scans, ~16 sec):



As deutero solvents can be a prohibitive cost in some undergraduate education programs, the ^{1}H NMR spectrum was also acquired in $CHCl_3$. The resultant *trans-* to *cis-* ratio is approximately the same (*i.e.*, 96 : 4).



(E) 95.74% ***(Z)*** 4.26

Dichloromethane (δ = 5.32 ppm) would also be a good proteo-solvent for this integration as the resonance would be even further removed from the area of interest (δ = 5.75-8.0 ppm).

Discussion & Conclsions

The Wittig reaction can easily be performed in a standard 3 hour undergraduate laboratory in the absence of solvent using (carbethoxymethylene)triphenylphosphorane as the Wittig reagent. We have demonstrated its reaction with benzaldehyde to afford ethyl cinnamate in quantitative yield in 10-15 minutes, but other benzaldehyde derivatives (*e.g., p-*methoxy or *p-*nitro) could also be used. The product can be extracted with hexane and characterized using ^{1}H NMR. ^{31}P{^{1}H}, COSY and JRES experiments can also be useful teaching tools to show students the power of NMR Spectroscopy for understanding reactions, products and stereochemistry.

The assignment of the isomers can be confirmed using: *(i)* the magnitude of observed coupling constants; *(ii)* ^{1}H NMR prediction software; or *(iii)* correlation with basic computation results. The observed isomeric ratios were the same at both 60 and 400 MHz instruments with either proteo- or deutero- solvents.

References

[1] Nguyen, K. C.; Weizman, H. *J. Chem. Educ.* **2007**, *84*(1), 119; Speed, T. J.; McIntyre, J. P.; Thamattoor, D. M. *J. Chem. Educ.* **2004**, *81*(9), 1355
[2] Courtesy of Len Mueller University fo California Riverside
[3] Robiette, R.; Richardson, J.; Aggarwal, V. K.; Harvey, J. N. *J. Am. Chem. Soc.* **2005**, *127*, 13469

For additional ideas of how to incorporate the NMReady-60 family of spectrometers into undergraduate teaching, please see:

Concentration Determination by Standard Addition
Synthesis of Biodiesel
Unknown Identification by ^{1}H NMR Spectroscopy
Aldol Condenation

available at:
www.nanalysis.com/experiments.html