

Synthesis of *trans*-9-(2-phenylethenyl)anthracene Supplementary Material

This experiment proposal was tested by more than four hundred students of introductory organic chemistry in the last three years to illustrate a Wittig reaction¹. The synthesis of a fluorescent compound increases the interest of all students for this kind of experiments. Experimental procedure can be easily performed by them, but the liquid-liquid extraction with dichloromethane requires the use of fume hoods. The reaction can be followed easily by TLC under ultraviolet lamp. This work is a great example to illustrate stereoselectivity of Wittig reaction where only one isomer is obtained. The stabilization of conjugate bases can be discussed once the Wittig salt produced in this reaction reacts easily with sodium hydroxide to the ylid in which the negative charge is stabilized by phosphorus and in this case by the aromatic ring. Additionally allows discussing fluorescence and chemiluminescence phenomena.

Additional notes on *trans*-9-(2-phenylethenyl)anthracene

The reaction is performed in a round-bottom flask with pressure-equalizing dropping funnel instead Erlenmeyer flask to prevent dichloromethane evaporation and inhalation (Scheme **SM 9.2.1.1**). It was found in literature a similar experimental procedure where dichloromethane was replaced by *N,N*-dimethylformamide². Product recrystallization may be carried out from ethanol instead isopropanol but a large volume of this solvent is required.



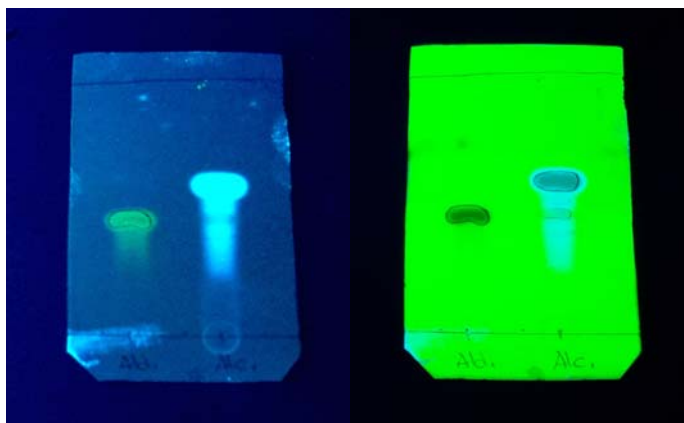
Scheme **SM 9.2.1.1** – Reaction set-up apparatus for *trans*-9-(2-phenylethenyl)anthracene preparation.

The other reaction product, triphenylphosphine oxide remains in mother liquors and can be recovered distilling most of the solvent followed by addition of petroleum ether (40-60°)³. *Trans*-9-(2-phenylethenyl)anthracene (Scheme **SM 9.2.1.2**) is obtained around 55% yield and melting point 125-133°C (130-132°C⁴) with temperature range lower than 2°C.



Scheme **SM 9.2.1.2** – Thin yellow plates of *trans*-9-(2-phenylethenyl)anthracene.

Development of chromatogram reveal single spot for 9-antraldehyde with $R_f = 0.50$ and product spot with $R_f = 0.75$. When irradiated at 366 nm only product spot turns bright blue. Spot of 9-antraldehyde can be usually detected in the final product². Traces of aldehyde can be also easily identified by IR analysis.



Scheme **SM 9.2.1.3** – Chromatogram showing spots of 9-anthaldehyde (left) and *trans*-9-(2-phenylethenyl)anthracene (right) under ultraviolet lamp (366 and 254 nm).

Dilute ethanol solution of *trans*-9-(2-phenylethenyl)anthracene under ultraviolet lamp shows strong fluorescence (Scheme **SM 9.2.1.4**).



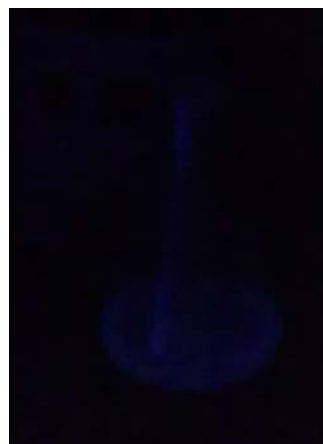
Scheme **SM 9.2.1.4** – Dilute ethanol solution of *trans*-9-(2-phenylethenyl)anthracene under ultraviolet lamp.

Quemiluminescence⁵ reaction was performed using a peroxyoxalate system with bis(2,4,6-trichlorophenyl oxalate) and sodium acetate⁶ in the presence of *trans*-9-(2-phenylethenyl)anthracene. The addition of hydrogen peroxide results in a light-blue color emission that lasts for several minutes (Scheme **SM 9.2.1.5**).



Scheme **SM 9.2.1.5** – Quemiluminescence reaction using bis(2,4,6-trichlorophenyl oxalate).

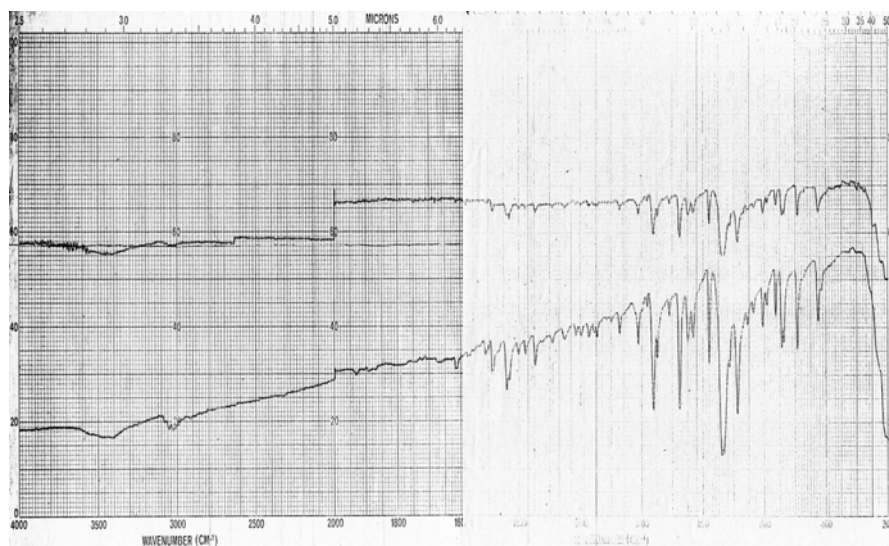
This reaction can also be carried out using oxalyl chloride with short emission of light-blue color (about 10 seconds) followed by purple light emission⁷ (about 15 to 30 seconds) (Scheme **SM 9.2.1.6**).



Scheme **SM 9.2.1.6** – Quemiluminescence reaction using oxalyl chloride

IR spectra:

Students easily identify a strong band at 960 cm^{-1} due to the *trans* group. IR spectrum of *trans*-9-(2-phenylethenyl)anthracene is available in literature⁸.



Scheme **SM 9.2.1.7** - IR (KBr) of *trans*-9-(2-phenylethenyl)anthracene.

NMR spectra:

The students analyzed the NMR data available in literature². As expected, the vinylic protons produce a pair of doublets with a large constant coupling ($J = 17\text{ Hz}$) confirming the *trans* structure. One of these is clearly separated from the signal corresponding to the fourteen aromatic protons. The other doublet is embedded in the aromatic signal.

¹ C. A. M. Afonso, D. P. Simão, L. P. Ferreira, M. S. Serra, M. M. M. Raposo, *100 Experiências de Química Orgânica*, IST Press, 2011, 199.

² a) C. Jaworek e S. Iacobucci, *J. Chem. Ed.*, 2002, **79**, 111; b) A. M. Jacob, Ph.D. Thesis, http://shodhganga.inflibnet.ac.in/bitstream/10603/5851/8/08_chapter%202.pdf, access in May 2015.

³ Silversmith, E. F., *J. Chem Ed.*, 1986, **7**, 645.

⁴ H. Becker, K. Andersson, *J. Org Chem.*, 1983, **48**, 4542.

⁵ <http://www.scienceinschool.org/2011/issue19/chemiluminescence>, access in May 2015.

⁶ A. G. Hadd, D. W. Lehmpuhl, L. R. Kuck and Galen P. Mell, *J. Chem. Educ.*, 1999, **76**, 1237.

⁷ R. Albertin, M. Arribas, E. Bastos, S. Röpke, P. Sakai, A. Sanches, C. Stevani, I. Umez, J. Yu e W. Baader,

Química Nova, 1998, **21**, 772.

- ⁸ a) <http://webbook.nist.gov/cgi/cbook.cgi?Spec=C1895983&Index=0&Type=IR&Large;> , access in May 2015.
b) <http://webbook.nist.gov/cgi/cbook.cgi?ID=C1895983&Mask=80#IR-Spec> , access in May 2015.

Synthesis of 4-vinylbenzoic acid

Supplementary Material

This experiment was performed and tested by undergraduate students to illustrate an ylide formation and Wittig reaction. Acid-base reactions can be also discussed once the phosphonium salt produced in this reaction reacts easily with sodium hydroxide to the ylide because is stabilized by resonance. Wittig reactions are only sometimes stereoselective and mixture of *E* and *Z* isomers may result. In this work only one isomer is obtained due to the use of formaldehyde as carbonyl compound. Answering to the question 4 of additional question: if benzaldehyde was used instead formaldehyde, both *E* and *Z* isomers should be obtained. Experimental procedure can be easily performed by students, but requires the use of fume hoods.

Additional notes on the preparation of 4-carboxybenzyltriphenylphosphonium bromide:

4-(Bromomethyl)benzoic acid can be either purchased, or prepared according to another experimental procedure described in this book. The reflux set-up is shown in figure **SM 9.2.2.1**. The initially clear solution quickly became cloudy and the phosphonium salt that precipitated was obtained after vacuum filtration (figure **SM 9.2.2.2**) with an average yield of 75-85% and used without further purification. More product can be obtained by evaporation of mother liquor. The melting point reported in literature is high (298-300 °C¹) and out of range of the available melting point apparatus (230°C), so students verified instead if the product remained solid at that temperature.



SM 9.2.2.1 – Reflux set-up



SM 9.2.2.2: Vacuum filtration apparatus

Additional notes on the preparation of 4-vinylbenzoic acid:

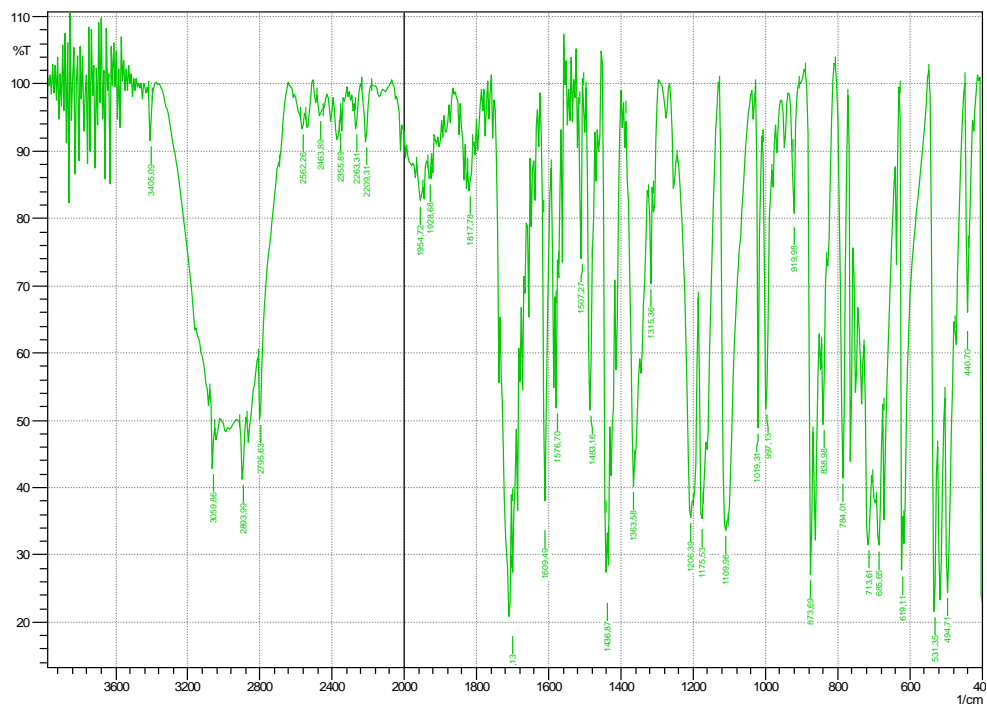
Triphenylphosphine oxide is a side product that precipitates during the reaction and it is separated by filtration. 4-Vinylbenzoic acid is recrystallized from aqueous ethanol (7:3) (figure **SM 9.2.2.3**) with an average yield of 15-25%. The recorded melting point is between 138 and 140 °C with a maximum melting point range of 2° C (literature: 142-145° C¹).



SM 9.2.2.3 – Copper funnel (previously heated by flame) for hot filtration

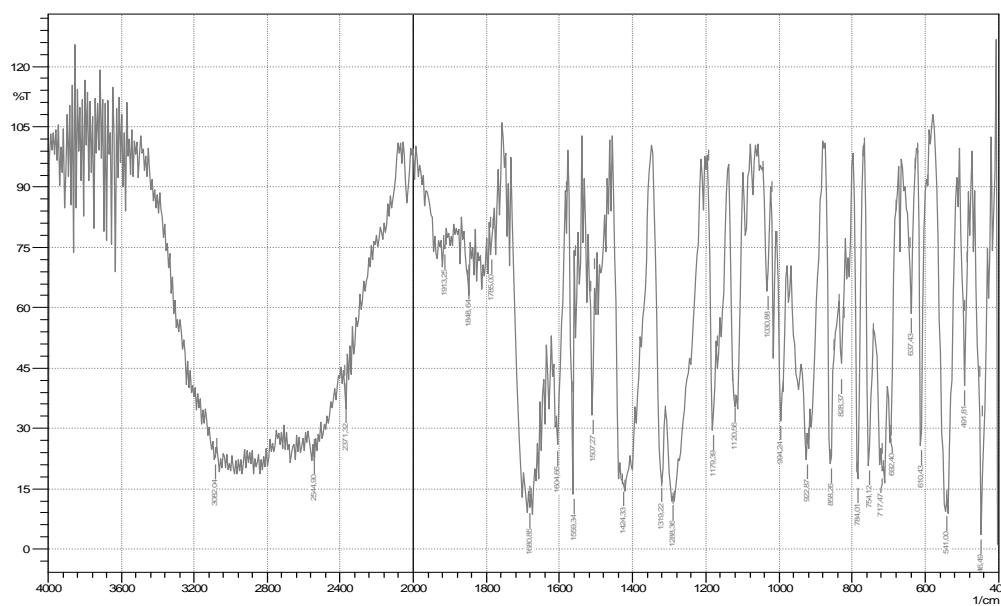
IR spectra:

Students easily identify a strong band due to C=O group at 1700 cm⁻¹ for 4-carboxybenzyltriphenylphosphonium bromide (Figure **SM 9.2.2.4**) and at 1680 cm⁻¹ for 4-vinylbenzoic acid (Figure **SM 9.2.2.5**).



SM 9.2.2.4: IR (KBr) of 4-carboxybenzyltriphenylphosphonium bromide

IR spectral data for 4-carboxybenzyltriphenylphosphonium bromide can be found in literature¹. The IR spectrum of 4-vinylbenzoic acid is also available on SDBS under number 24006².



SM 9.2.2.5: IR (KBr) of 4-vinylbenzoic acid

NMR spectra:

The students analyzed the NMR data available in literature for both products¹. As expected, three signals can be observed due to the vinylic system for 4-vinylbenzoic acid as well as aromatic protons and OH proton.

¹ L. F. Tietze, T. Eicher, *Reactions and Synthesis in the Organic Chemistry Laboratory*, University Science Books, 1989, 179.

² http://sdbs.db.aist.go.jp/sdbs/cgi-bin/cre_index.cgi, access in Sep 2015.

Preparation of nitrostilbenes by Wittig reaction

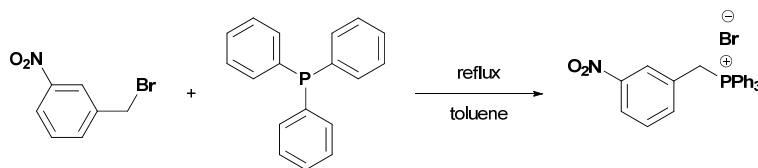
Supplementary Material

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Experiment notes

The objective of this experimental work is to introduce the students to a simple synthesis of unsymmetrical stilbenes *via* the Wittig reaction. The experiment is multifaceted and can be used to teach students about alkene synthesis, phase transfer catalysis, the use of ¹H NMR, to characterize the mixture of diastereomers, as well as the isolated products.

The phosphonium salt used in the experiment was synthesized in our lab from the reaction of 3-nitrobenzylbromide (1.85 mmol) with triphenylphosphine (1.85 mmol) in toluene (1 mL) under reflux (2 hours) (**Scheme SM 9.2.3.1**).



Scheme SM 9.2.3.1- Reaction scheme for the synthesis of phosphonium salt

For most of the compounds *Z/E* ratios could be determined based on the doublet integration of the olefinic protons peaks of the isomers after flash chromatography. These peaks could be identified by the chemical shifts given in part per million (ppm) and by characteristic coupling constants given in hertz: ¹H NMR (CDCl₃, 300 MHz) δ: for (*Z*)-1-(4-methoxystyryl)-3-nitrobenzene 6.56 (1H, d, *J* = 12), 6.75 (1H, d, *J* = 12); for (*E*)-1-(4-methoxystyryl)-3-nitrobenzene, 7.06 (1H, d, *J* = 16.5), 7.25 (1H, d, *J* = 16.5);

for (Z)-1- (4-chlorostyryl)-3-nitrobenzene 6.65 (1H, d, $J = 12$), 6.74 (1H, d, $J = 12$), for (E)-1- (4-chlorostyryl)-3-nitrobenzene 7.13 (1H, d, $J = 16$), 7.41 (1H, d, $J = 16$) (**Fig. SM 9.2.3.8 and Fig. SM 9.2.3.9**).

Calculations:

Ratio of Z isomer = integration of both olefinic Z protons X 100/ integration of (Z+E) olefinic protons.

Ratio of E isomer = integration of both olefinic E protons X 100/ integration of (Z+E) olefinic protons.

Example for the 1- (4-chlorostyryl)-3-nitrobenzene (**Fig. SM 9.2.3.9**):

$$\text{ratio Z isomer} = (2.0 \times 100 / (2.0 + 0.16^* + 0.33^* + 0.34^* + 0.22^*))$$

$$\text{ratio E isomer} = (1.05^\# \times 100 / (2.0 + 0.16^* + 0.33^* + 0.34^* + 0.22^*))$$

*- integration values for both doublets of the olefinic protons of the E isomer

#. Sum integration of E doublets

The greater difficulty is the identification and integration of protons of the E isomer as sometimes they are mixed with the aromatic protons, but for identification, coupling constants could help in this task. For the integration values the task could be more difficult if the peaks are not individualized.

For compound 1-(4-methoxystyryl)-3-nitrobenzene (**Fig. SM 9.2.3.8**) the Z/E ratio could be obtained either from the integration of olefinic protons or more easily from the integration of methoxy group signal of both isomers.

Example:

$$\text{ratio Z isomer} = (2.9 \times 100 / (2.9 + 1.32))$$

$$\text{ratio E isomer} = (1.32 \times 100 / (2.9 + 1.32))$$

The NMR spectra for several nitrostilbenes were previously reported and students could compare their values with this data.¹

The method is also a very good example to teach students about the concept of retrosynthetic analysis since they can use different aldehydes and ylides to reach the final products. Another advantage of the experiment is that the reagents are common in the lab and generally not expensive.

One interesting aspect of this experiment is that normally the carbanion/ylides are colored, (brown, red-brownish or red) and the products are normally, yellow or pale yellow, thus it is possible to monitor the Wittig reaction progression by color changes (**Fig. SM 9.2.3.1**). As reactions proceed in phase transfer conditions vigorous stirring is used along the process.

Depending on the reactants, the stirring velocity, and the time of reaction, nearly quantitative yields can be achieved.

The reaction can be conducted at micro or preparative-scale ranging from 10 μ M to 100 mM.

The experiment could also be easily performed with microwave irradiation with fast and good results. Described experimental procedure could be directly implemented considering the micromolar range of the reaction¹.

The reproducibility of the experiment was assessed by undergraduate and graduate students in the Medicinal Chemistry Department of Faculty of Pharmacy, University of Lisbon.

Table SM 9.2.3.1- Results obtained by graduate and undergraduate students

		Yield (%)	Z/E
Graduate students (4)*	1- (4-methoxystyryl)-3-nitrobenzene	96-98	77:23
Undergraduate students (10)*	1- (4-methoxystyryl)-3-nitrobenzene	39-89	70:30
Graduate students (4)*	1- (4-chlorostyryl)-3-nitrobenzene	89-93	70:30
Undergraduate students (10)*	1- (4-chlorostyryl)-3-nitrobenzene	65-79	65:35

* number of students

In the TLC analysis of the reaction mixture is possible to see a yellow spot (signed with a red arrow) corresponding to nitrotoluene, a side product of the reaction that results from hydrolysis of the phosphonium salt or ylide. The spots signed with the blue arrows are the diastereoisomers formed in the reaction and the spot with the lower R_f is the starting aldehyde (**Fig SM 9.2.3.2**).

Photos of the experiment



Figure SM 9.2.3.1 - Reaction mixture at time 0, 30 minutes and at the end of reaction. Note the red-brownish color gradually fading along the time

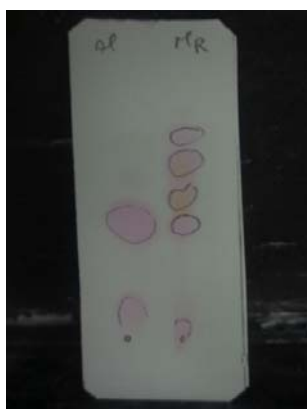


Figure SM 9.2.3. 2 - TLC analysis of reaction mixture (hexane:ethyl ether 4:1)
Al: starting aldehyde, MR: reaction mixture .



Figure SM 9.2.3.3 - Liquid-Liquid extraction

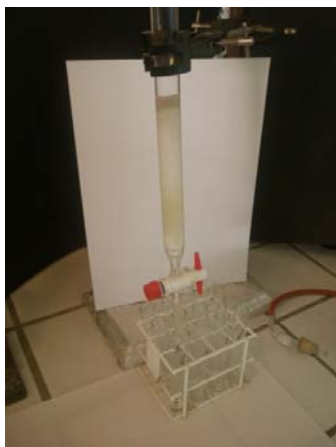


Figure SM 9.2.3.4 - Flash Chromatography



Figure SM 9.2.3.5 - Isolated *Z/E* mixture. Product is a yellow gum.

Spectra

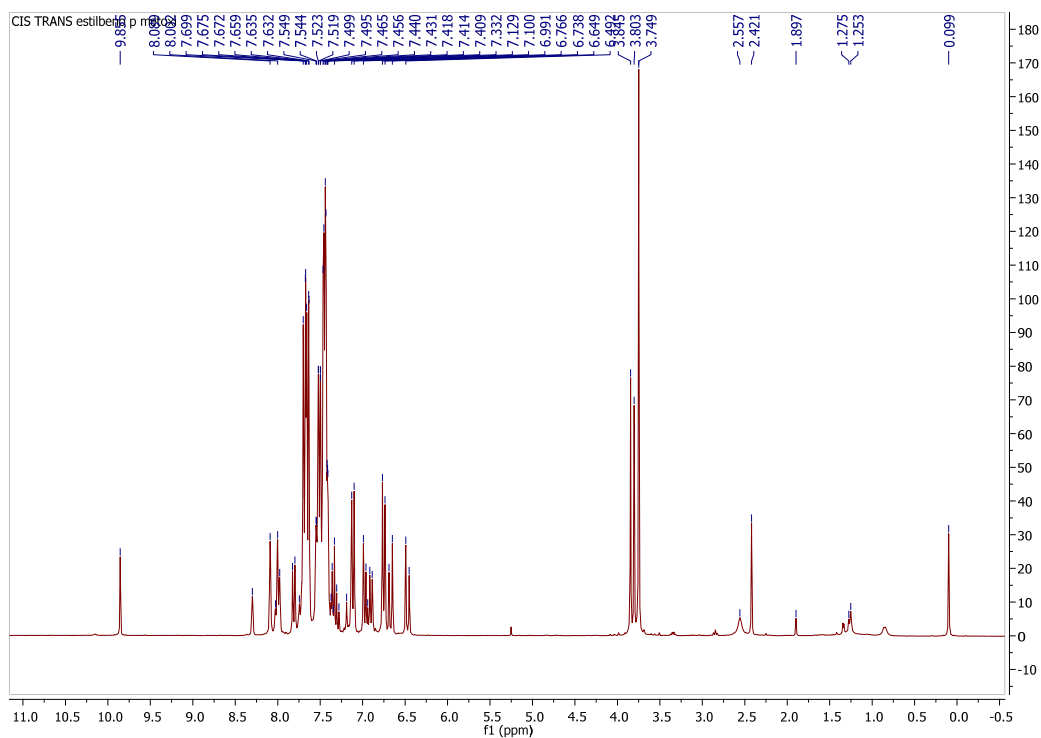


Figure SM 9.2.3.6 - ^1H NMR of reaction mixture of 1-(4-methoxystyryl)-3-nitrobenzene. At $\delta = 9.8$ is possible to observe the aldehydic proton of the 4-methoxybenzaldehyde as well as three peaks for the OMe group corresponding to both the Z/E isomers and the starting aldehyde.

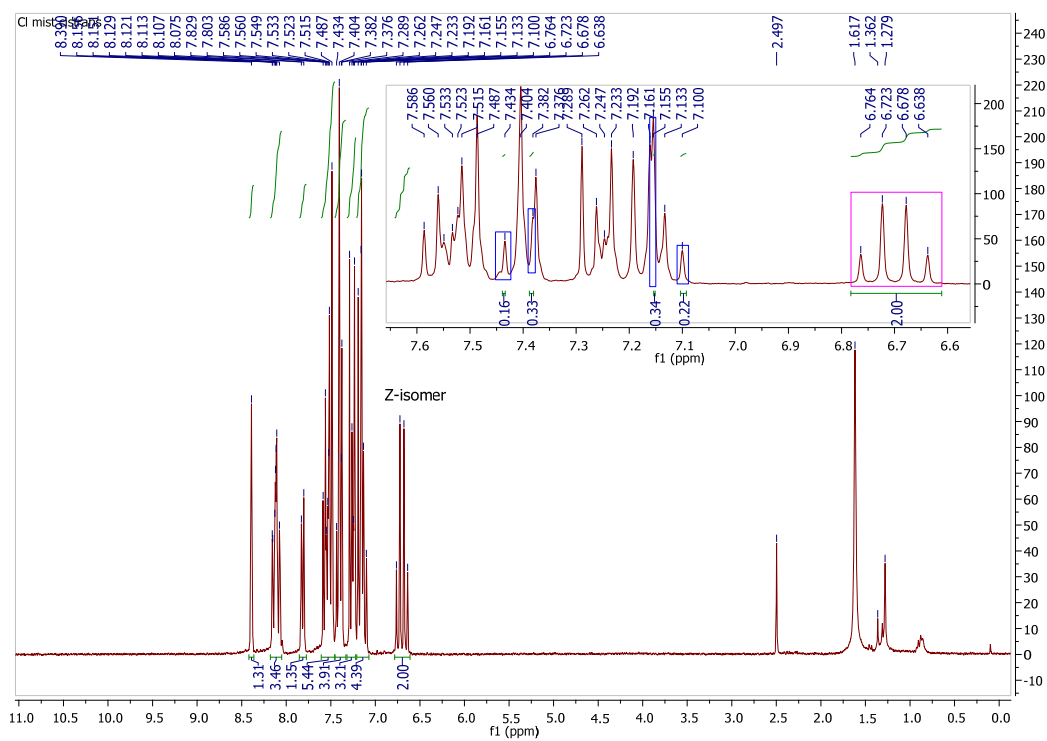


Figure SM 9.2.3.9 - ^1H NMR of 1-(4-chlorostyryl)-3-nitrobenzene (Z/E mixture). Olefinic protons of the Z isomer in magenta and the olefinic protons of the E isomer in blue

1. T. Rodrigues, F. Lopes and R. Moreira, *Synth. Commun.*, 2012, **42**, 747.

Building an alkene spacer by Wittig reaction: the synthesis of 4-[2-(4-nitrophenyl)ethenyl]benzonitrile

Supplementary Material

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Experimental Notes

This experiment aims to synthesize a new carbon-carbon double bond which link two aromatic molecules used as starting materials, using the Wittig synthetic method. The Wittig reaction has a wide applicability and reliability and their reagents are common in a laboratory: an alkyl or benzyl halide, a triarylphosphine (or a trialkylphosphine) and an aldehyde or a ketone; so this reaction can easily be done. This reaction presents several advantages in an Organic Chemistry course since it can be explored in different perspectives and deals with several concepts. The formation of a new double bond, connecting the two reagents and leading to an extended carbon chain; the stereocontrol limitation that could be used to develop the *E/Z* isomerism concept and the isomeric ratio determination are examples of this versatility. The influence of other factors (solvent, temperature, ylides substituents) could also be explored.

This experiment is easy to conduct despite the use of a reflux apparatus and the safety precautions due to the reagents and solvents. The reagent quantities can be changed without loose the quality of results.

In addition to the synthesis of the final product, it is also proposed the preparation of the phosphonium salt. Its synthesis usually affords excellent yields (80-95%). However, this session can be omitted if a phosphoranylidene commercially available is used.

Other alternative solvents can be used but since the phosphonium salt is not soluble in toluene, this solvent allows the precipitation of the product.

The use of diethyl ether to wash the phosphonium salt facilitate the removal of toluene and the drying of the solid. If a dry solid is urgently needed, the drying process can be done under reduced pressure (e.g., vacuum pump apparatus or even at the rotary evaporator); otherwise, in can be done at a

common glass dessicator. The phosphonium salts usually are hygroscopic but this product remains with quality for more than six months.

The method proposed for Wittig reaction can use other aldehydes (available or interesting for other purpose) with good results, but it could be necessary to change solvent, temperature or time of reaction.

The method described usually affords the product in good yield (70-80%) with an up to 85:15 *E/Z* isomeric ratio, but it depends on the conditions. The yield and isomeric ratio depend on the temperature. The reaction can be done at room temperature but the yield drops to one half of obtained with reflux and the *E/Z* ratio decreases.

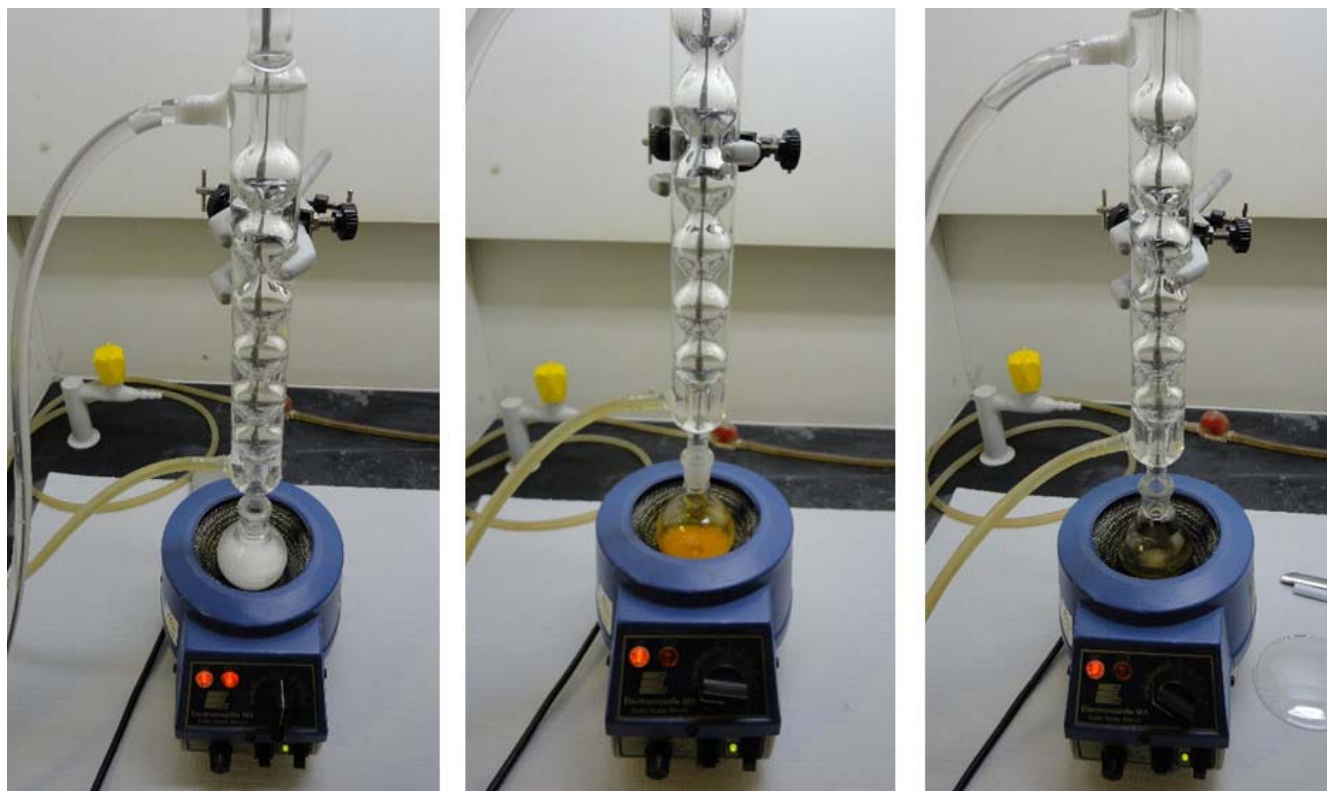
Also, depending on the duration of the session, the Wittig reaction can be performed in 2 h or 3 h. Much longer times usually do not increase significantly the yield of the reaction.

The isolation of the *E* isomer is optional and can be done if the session is long enough; the proposed time is enough for students with some experience at lab. However, this procedure is not strictly necessary for the introduction of all the concepts. The purification of *E* isomer allows the full characterization of this compound, including the record of ^1H and ^{13}C NMR spectra, to compare with the spectra of *E/Z* mixture obtained before.

The isolation of the *Z* isomer is not proposed in this experiment. This can be obtained by column chromatography, but this is not considered in the classroom experiment since it is a more expensive technique and also more time consuming.

This work was carried out at a 3rd year curricular unit at a Chemistry degree course, by a small number of students, generally 1-2 groups, with some experimental lab skills. The reagents were chosen to reach a product that could be used in subsequent experimental procedures.

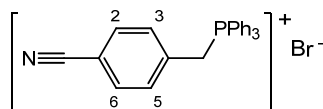
This experiment is very versatile and allows, with small changes and adaptations, the maintenance of the proposed objectives while it can be used to prepare useful products. Also, if is intended by the instructor, the quantity prepared at session 1 can be used to repeat the session 2 or to perform a reaction with a different aldehyde, with the possibility to develop other concepts, or session 1 could done in a more small scale.



Scheme SM 9.2.4.1 Reaction setup apparatus: (from left to right) synthesis of (4-cyanophenyl)methyltriphenyl-phosphonium bromide (session 1); after the addition of potassium *tert*-butoxide to (4-cyanophenyl)-methyltriphenylphosphonium bromide (session 2); after the addition of 4-nitrobenzaldehyde to the previous reaction mixture (session 2).

Experimental data¹ and spectra

- Experimental data for (4-cyanophenyl)methyltriphenylphosphonium bromide



White solid.

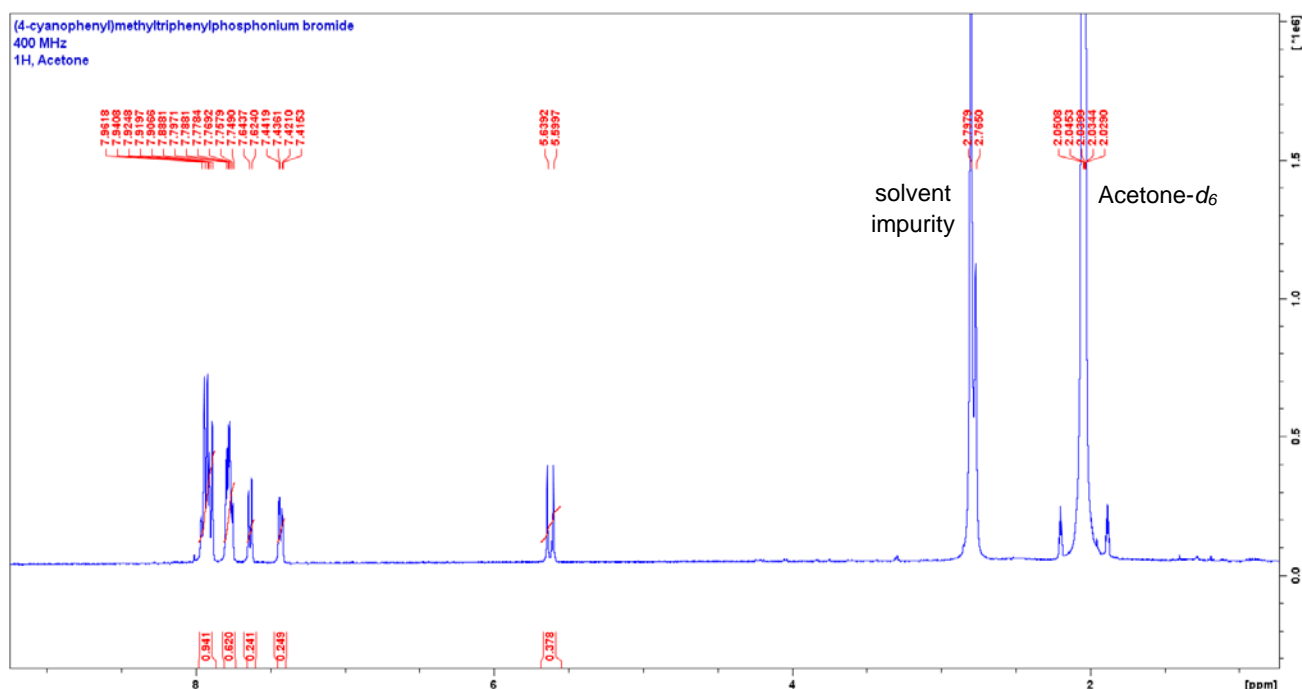
Yields: 80-95%.

¹H NMR, δ /ppm ((CD₃)₂CO): 5.62 (d, 2H, ²J_{HP}=15.8, PCH₂), 7.43 (dd, 2H, J=8.3 and 2.3, H₃,H₅), 7.63 (d, 2H, J=7.9, H₂,H₆), 7.75-7.80 (m, 6H, PPh₃:H_{meta}), 7.90 (d, 3H, J=7.4, PPh₃:H_{para}), 7.92-7.96 (m, 6H, PPh₃:H_{ortho}).

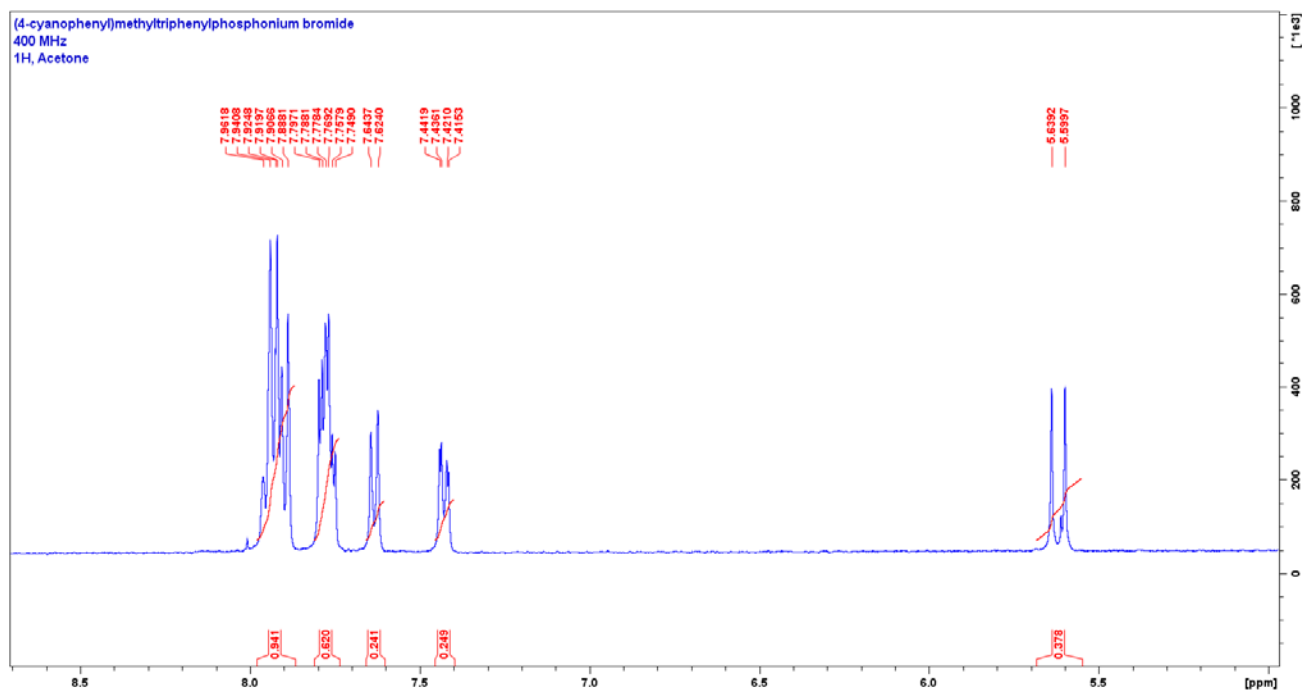
$^{31}\text{P}\text{-}\{^1\text{H}\}$ NMR, δ/ppm ($(\text{CD}_3)_2\text{CO}$): 25.24 (PPh_3).

IR ($\nu_{\text{max}}/\text{cm}^{-1}$) (KBr): 3076 (w), 3048 (w), 3010 (w), 2992 (w), 2970 (w), 2862 (m), 2849 (m), 2771 (m), 2506 (vw), 2416 (vw), 2267 (vw), 2226 (m), 2006 (vw), 1976 (vw), 1920 (vw), 1819 (vw), 1601 (m), 1588 (m), 1495 (m), 1487 (w), 1479 (w), 1435 (s), 1385 (w), 1341 (w), 1319 (w), 1259 (vw), 1194 (w), 1164 (m), 1111 (s), 1013 (w), 993 (m), 926 (vw), 864 (s), 833 (m), 751 (s), 744 (s), 720 (s), 690 (s), 616 (w), 563 (vs), 529 (s), 500 (s), 494 (s), 444 (m). (w- weak, m-medium, s-strong, v-very)

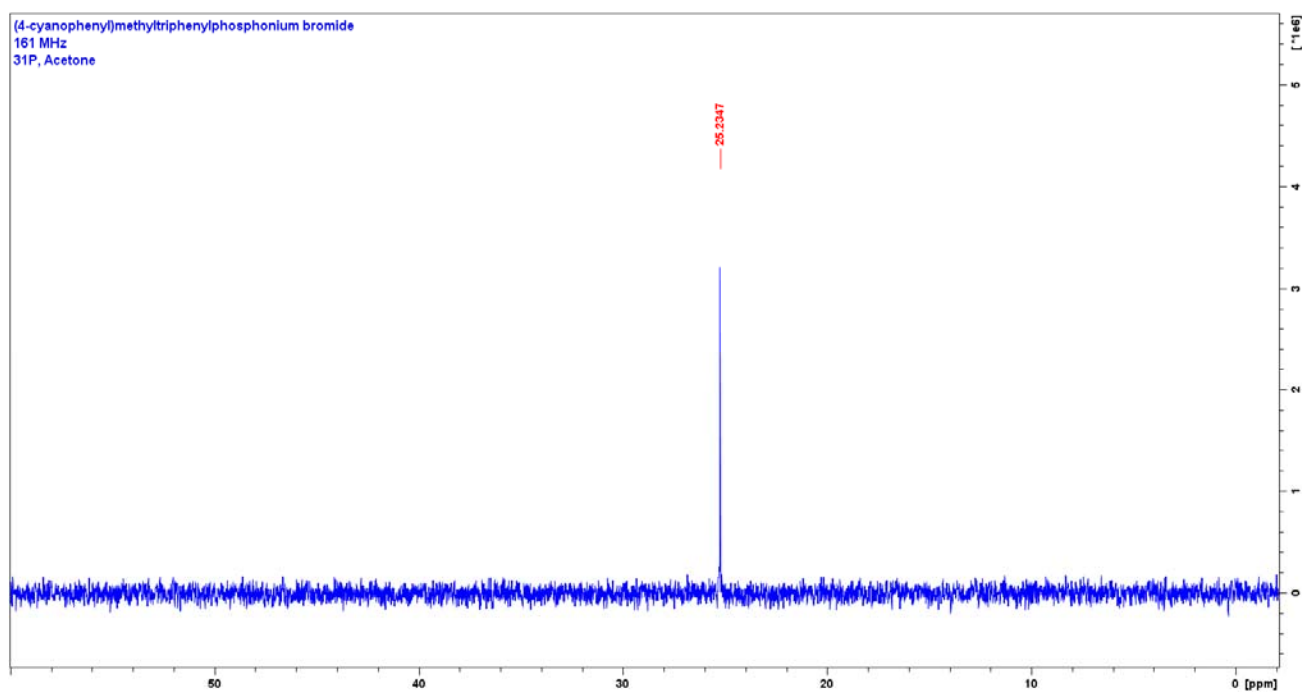
- Spectra of (4-cyanophenyl)methyltriphenylphosphonium bromide



Scheme SM 9.2.4.2 ^1H NMR spectrum (400 MHz, acetone- d_6) of the (4-cyanophenyl)methyltriphenylphosphonium bromide.

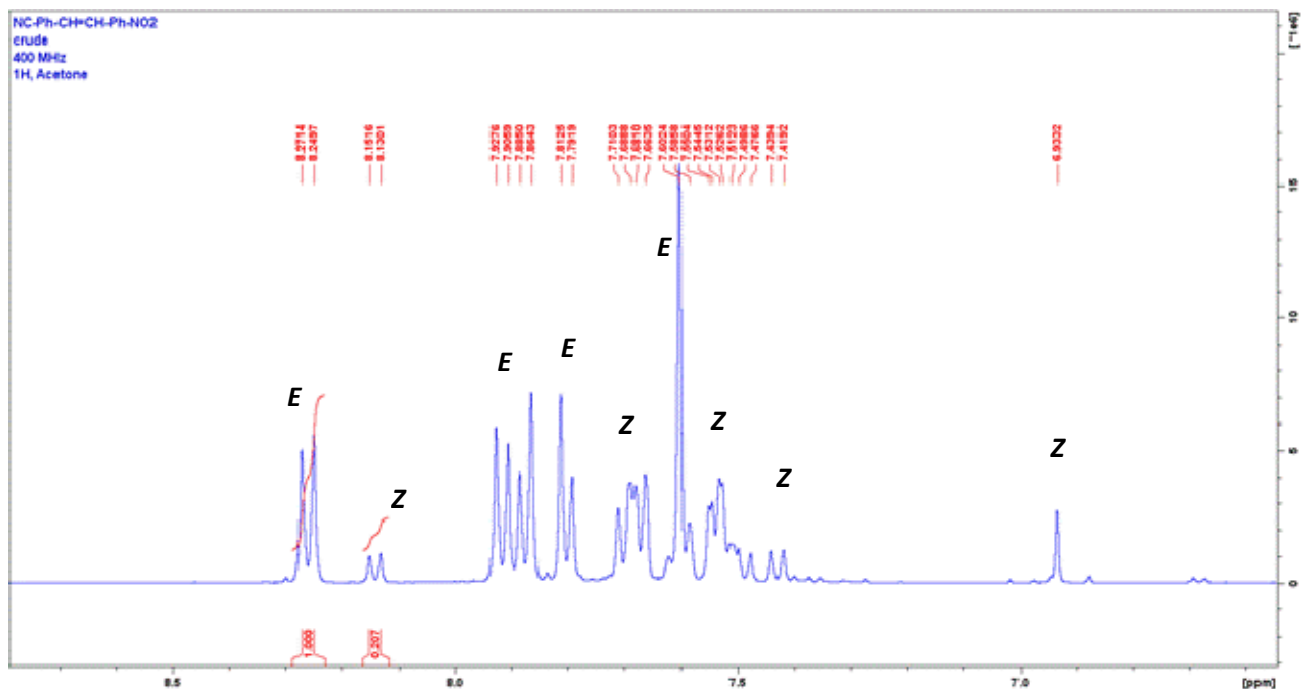


Scheme SM 9.2.4.3 ^1H NMR spectrum (400 MHz, acetone- d_6) of the (4-cyanophenyl)methyltriphenylphosphonium bromide (expansion between 5.0-8.7 ppm).



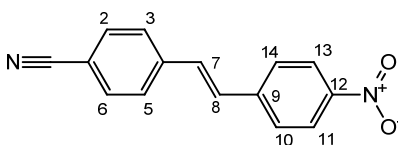
Scheme SM 9.2.4.4 ^{31}P NMR spectrum (161 MHz, acetone- d_6) of the (4-cyanophenyl)methyltriphenylphosphonium bromide.

- Spectra of a mixture of (E) and (Z) 4-[2-(4-nitrophenyl)ethenyl]benzonitrile



Scheme SM 9.2.4.5 ¹H NMR spectrum (400 MHz, acetone-*d*₆) of crude product showing a mixture of *E* and *Z* isomers of 4-[2-(4-nitrophenyl)-ethenyl]benzonitrile (*E*:*Z* isomers in a 83:17 proportion) (expansion between 6.6-8.4 ppm).

- Experimental data for (E)-4-[2-(4-nitrophenyl)ethenyl]benzonitrile



Yellow solid.

Yields: 70-80%.

m.p. 258-259 °C (dichloromethane) (lit.² 259-261 °C).

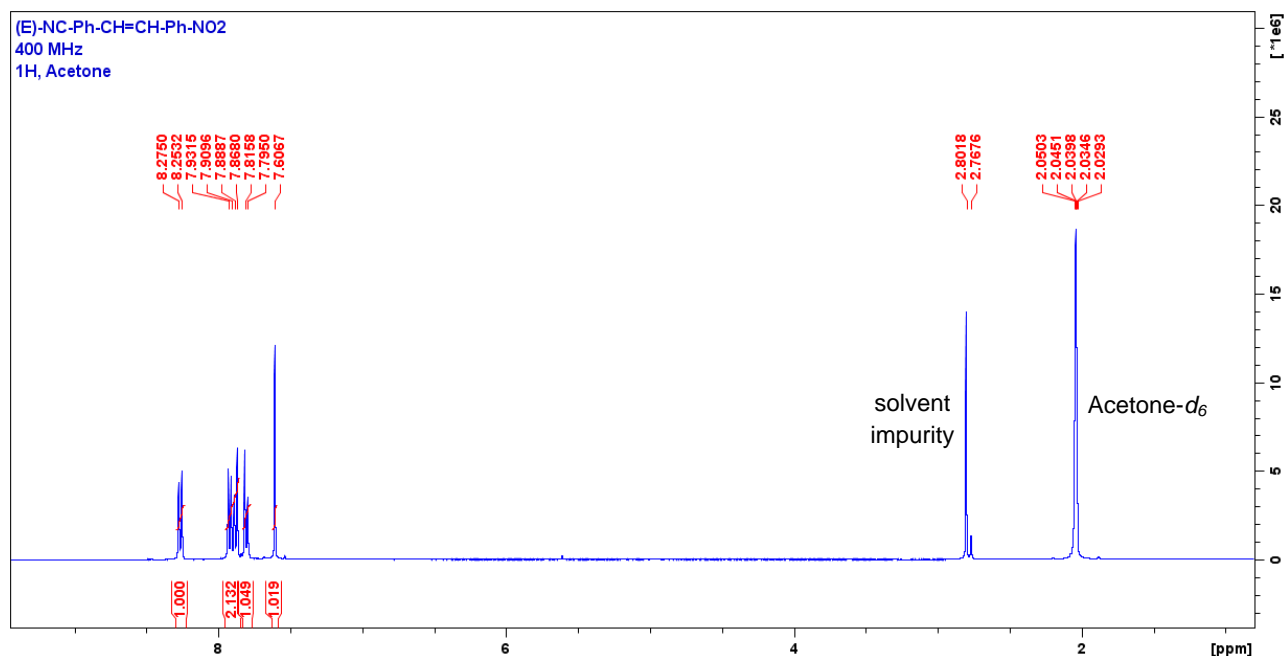
¹H NMR, δ/ppm (CD₂Cl₂): 7.30 (s, 2H, H7,H8), 7.66 (d, 2H, *J*=8.4, H3,H5), 7.70 (d, 2H, *J*=8.4, H2,H6), 7.71 (d, 2H, *J*=8.7, H10,H14), 8.24 (d, 2H, *J*=9.0, H11,H13). **δ/ppm ((CD₃)₂CO):** 7.61 (s, 2H, H7,H8), 7.81 (d, 2H, *J*=8.3, H3,H5), 7.88 (d, 2H, *J*=8.30, H2,H6), 7.92 (d, 2H, *J*=8.8, H10,H14), 8.26 (d, 2H, *J*=8.7, H11,H13).

¹³C NMR, δ/ppm (CD₂Cl₂): 112.10 (C1), 119.02 (NC), 124.46 (C11,C13), 127.73 (C3,C5), 127.77 (C10,C14), 130.09 (C7), 131.45 (C8), 133.00 (C2,C6), 141.00 (C4), 143.17 (C9), 147.71 (C12). **δ/ppm ((CD₃)₂CO):** 112.33 (C1), 119.28 (NC), 124.84 (C11,C13), 128.58 and 128.60 (C3,C5 and C10,C14), 130.85 (C7), 131.20 (C8), 133.46 (C2,C6), 142.07 (C4), 144.21 (C9), 148.23 (C12).

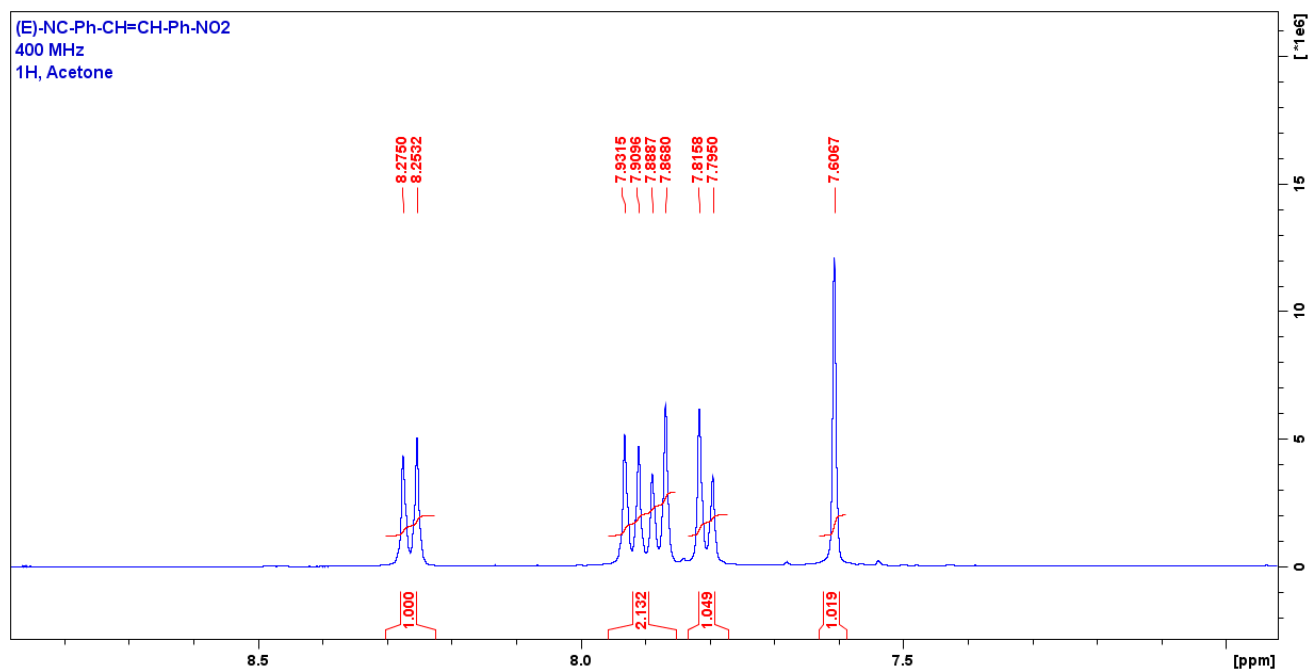
IR (ν_{max}/cm⁻¹) (KBr): 3037 (vw), 2924 (vw), 2830 (vw), 2218 (m), 1602 (s), 1591 (s), 1506 (s), 1414 (w), 1385 (w), 1372 (w), 1338 (vs), 1172 (w), 1103 (m), 972 (w), 953 (m), 875 (w), 846 (s), 815 (w), 712 (w), 718 (w), 683 (w), 548 (s), 504 (w). (w- weak, m-medium, s-strong, v-very)

MS (EI) *m/z*: 250 (M⁺), 220 (M⁺-NO), 203 (M⁺-NO₂H), 192 (220-CO), 190 (203-CH), 178 (M⁺- (NC+NO₂)), 176 (178-2H and C₁₀H₁₀NO₂⁺), 165 (C₁₃H₉⁺ and C₁₂H₇N⁺; base peak), 151 (C₁₂H₇⁺ and C₈H₉NO₂⁺), 140 (C₁₁H₈⁺ and NCC₉H₆⁺), 127 (NCC₈H₅⁺ and C₁₀H₇⁺), 102 (NCC₆H₄⁺ and C₆H₄C₂H₂⁺), 87 (C₇H₃⁺), 75 (C₆H₃⁺), 63 (C₅H₃⁺), 50 (C₄H₃⁺), 30 (NO⁺).

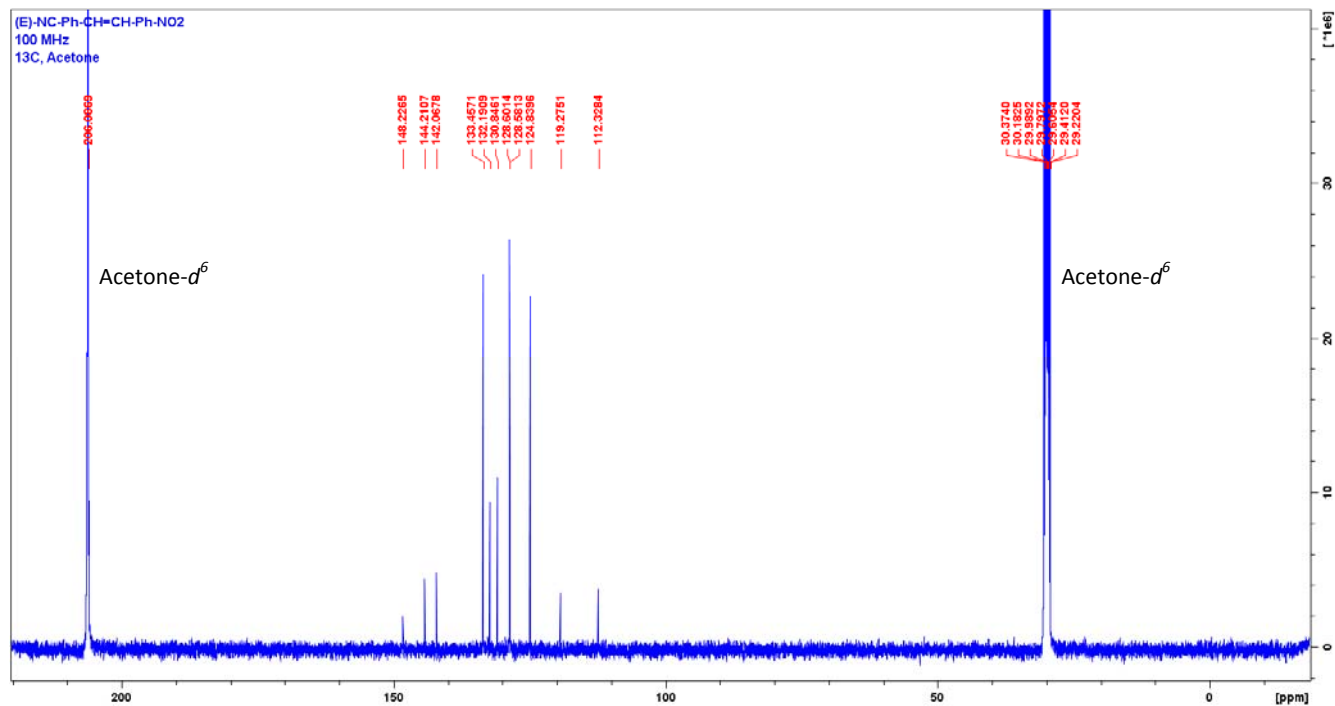
- Spectra of (*E*)-4-[2-(4-nitrophenyl)ethenyl]benzonitrile



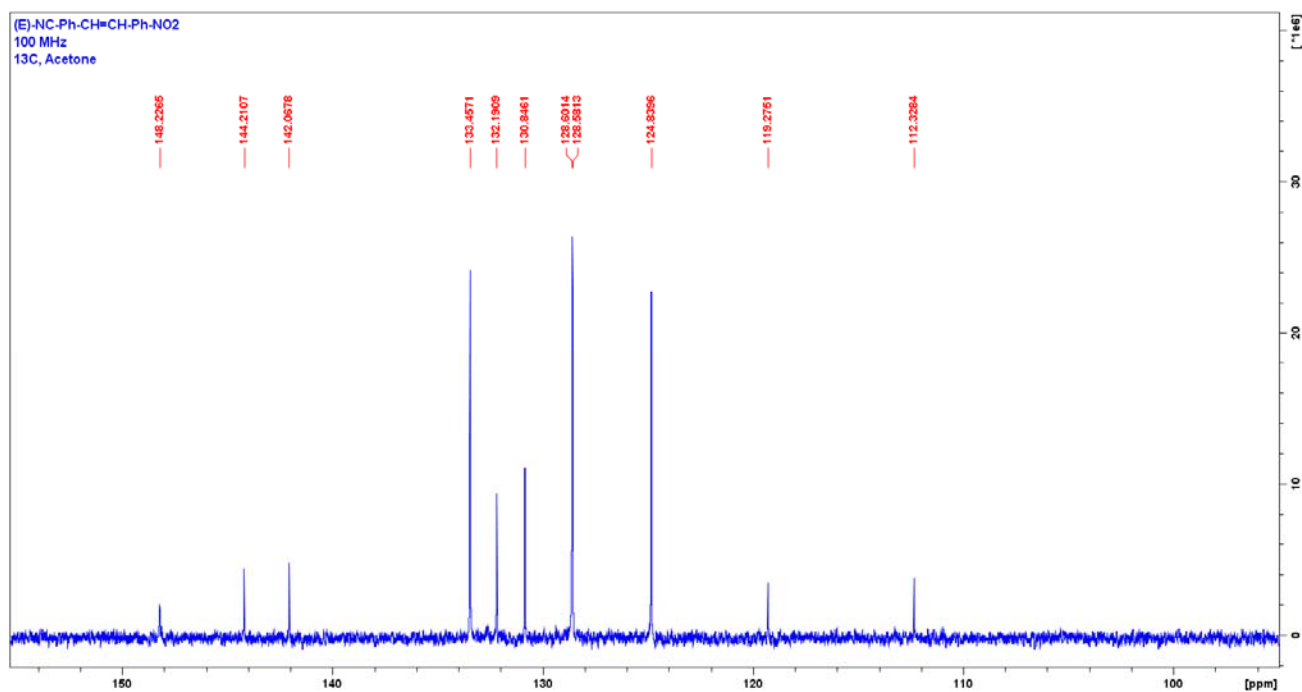
Scheme SM 9.2.4.6 ¹H NMR spectrum (400 MHz, acetone-*d*₆) of the *E* isomer of 4-[2-(4-nitrophenyl)ethenyl]-benzonitrile.



Scheme SM 9.2.4.7 ^1H NMR spectrum (400 MHz, acetone- d_6) of the *E* isomer of 4-[2-(4-nitrophenyl)ethenyl]-benzonitrile (expansion between 7.0-8.9 ppm).



Scheme SM 9.2.4.8 ^{13}C NMR spectrum (100 MHz, acetone- d_6) of the *E* isomer of 4-[2-(4-nitrophenyl)ethenyl]-benzonitrile.



Scheme SM 9.2.4.9 ¹³C NMR spectrum (100 MHz, acetone-*d*₆) of *E* isomer of 4-[2-(4-nitrophenyl)ethenyl]-benzotrile (expansion between 90-154 ppm).

¹ A. P. S. Teixeira, *Síntese de compostos derivados de ferro(II) com potenciais propriedades em óptica não linear*, PhD Thesis, Universidade de Évora, 2004, chapter 6, pp. 253-254.

² P. E. Hanna, R. E. Gammans, R. D. Sehon and M.-K. Lee, *J. Med. Chem.*, 1980, **23**, 1038-1044.

Preparation of *trans,trans*-distyrylbenzene by a Wittig reaction

Supplementary Material

Experiment Notes

Background information

Yield, melting point, IR

Table 1 – ^1H NMR data for *trans,trans*-distyrylbenzene

Figures

Photos of the experiment

^1H and ^{13}C NMR spectra of crude and purified products, including analysis of AB spectra

The procedure for this experiment has been developed for a Year 3 Organic Chemistry lab class at Heriot-Watt University. The experiment supports a lecture course where students are taught about the Wittig reaction.

The experiment has been used for over 5 years and is typically carried out by 15-20 students (about one third of the class). It provides a challenge for students to identify whether the Wittig reaction involving a benzylphosphonium salt produces a *cis* or a *trans* alkene or a mixture. The decision is made by comparison with the chemical shifts of two model compounds (*cis*- and *trans*-stilbene). A more thorough analysis should look at the ^1H NMR coupling constants observed for the alkene protons for which students need to correctly identify an AB spin system. The AB spin system, consisting essentially of two distorted doublets, is much easier to analyse than higher-order AA'BB' spin systems observed for other published examples of Wittig reactions, such as 1,4-diphenylbutadiene.^{1,2}

This makes the experiment different from cases where only a single isomer (usually with *trans* stereochemistry) is obtained in a Wittig reaction.^{3,4,5,6} The amount of *cis* isomer formed is high enough that the experiment avoids the need to use strong bases such as NaNH_2 or butyl lithium which can be a serious safety hazard in a teaching laboratory environment.

Step 1: Bis-phosphonium salt

Yield: The preparation of the bis-phosphonium salt generally presents no problems and follows a literature procedure.⁷ Typical student yields range from 61% to 99%, with an average of 90%. Samples can still contain traces of DMF which does not interfere with the subsequent Wittig reaction.

Step 2: Wittig reaction

Yield: Student yields of the Wittig product after recrystallisation tend to vary a lot: 4 – 78%, with an average of 47%. Losses occur usually during the recrystallisation step. The limiting reagent is the bis-phosphonium salt, so the theoretical yield of the distyrylbenzene product is 2.5 mmol corresponding to 0.71 g.

Recrystallisation in the presence of iodine converts the mixture of isomers into pure *trans,trans*-distyrylbenzene.⁸ The product is a yellow solid with a tell-tale greenish fluorescence (typical student m.p. 263 °C; lit. m.p. of 268-268.5 °C).⁷ If done incorrectly, students can end up with a mixture of isomers which will be immediately evident from a lower melting point (<200 °C). The quality of a student sample is readily apparent to an instructor from both the colour and the m.p. of the sample.

Students are generally provided with representative ¹H NMR spectra of the crude and recrystallised product. The reasons are three-fold: (i) making up NMR samples is more challenging due to the low solubility of the *trans,trans*-distyrylbenzene (ca. 2 mg per 0.7 mL of CDCl₃ or CD₂Cl₂); (ii) students who did not manage to obtain a single isomer can still analyse the NMR data; and (iii) to reduce the running costs for the lab (CD₂Cl₂ is much more expensive than CDCl₃).

TLC (petroleum ether/ethyl acetate, 5:1): $R_f = 0.48$ (*trans,trans*-distyrylbenzene)

Photos of the experiment

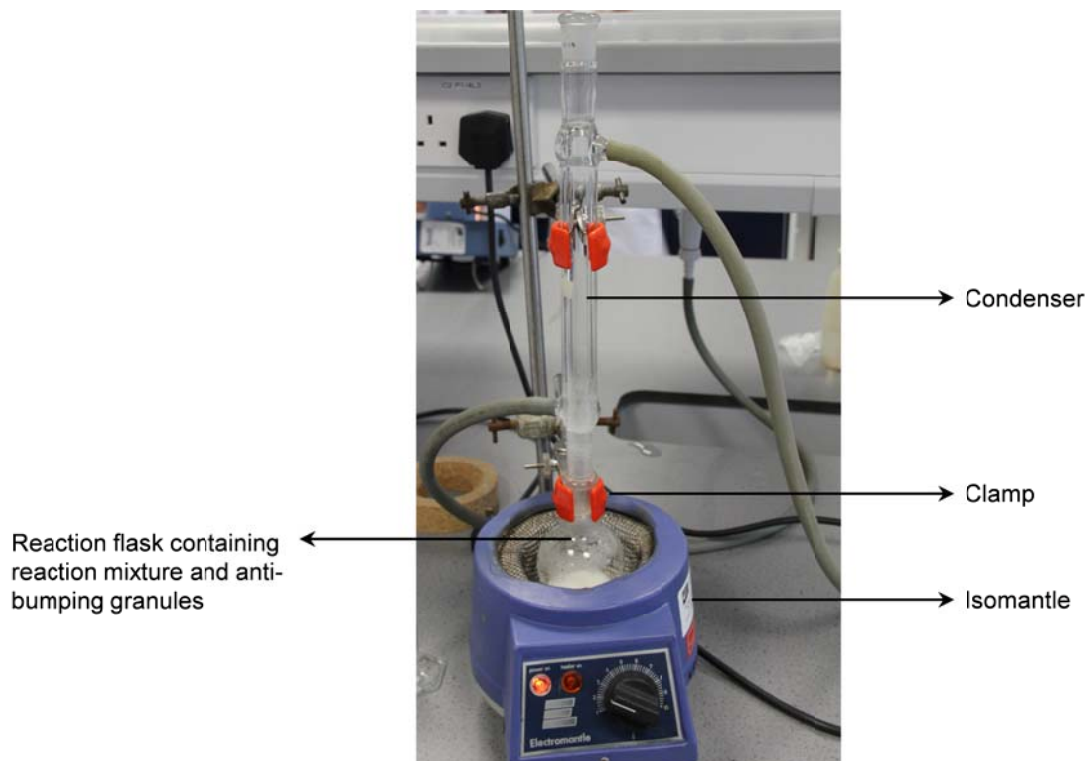


Figure SM 9.2.5.1 – Reaction mixture during the reflux step. The bis-phosphonium salt starts to precipitate after half an hour.

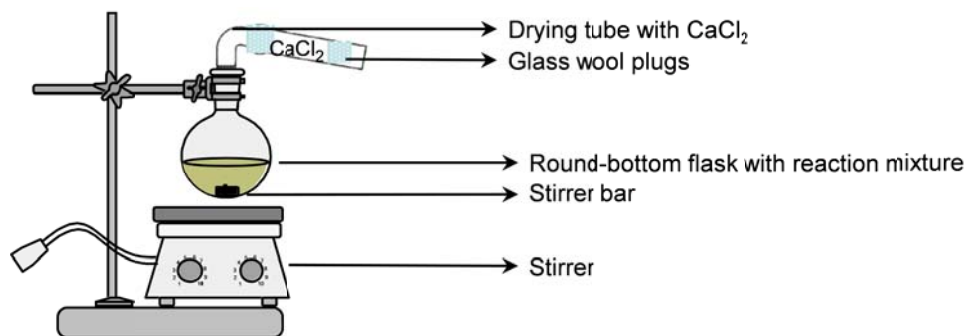


Figure SM 9.2.5.2 – Recommended set-up for carrying out the Wittig reaction.

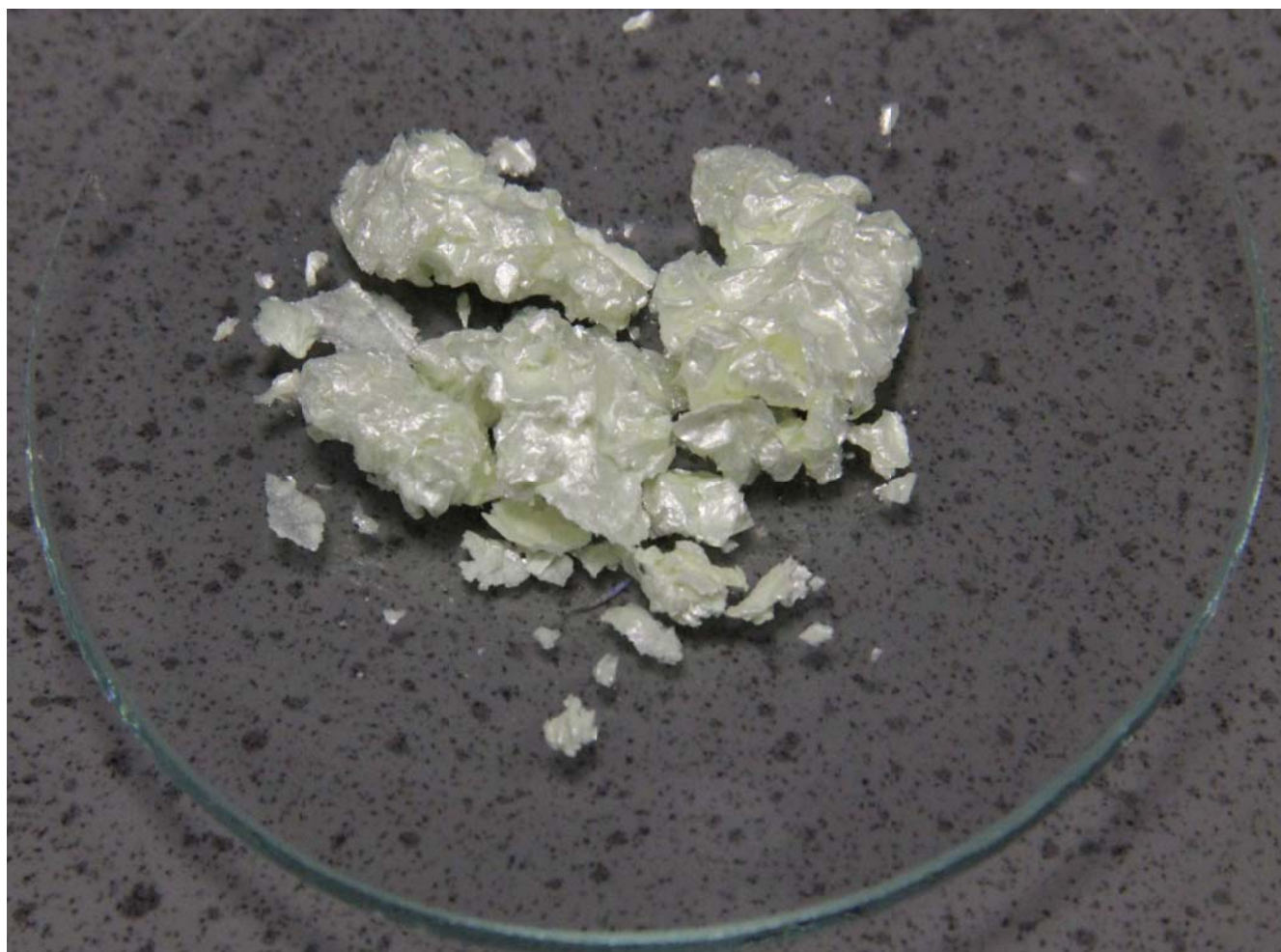


Figure SM 9.2.5.3 – Wittig product after recrystallisation and filtration.

¹H and ¹³C NMR spectra

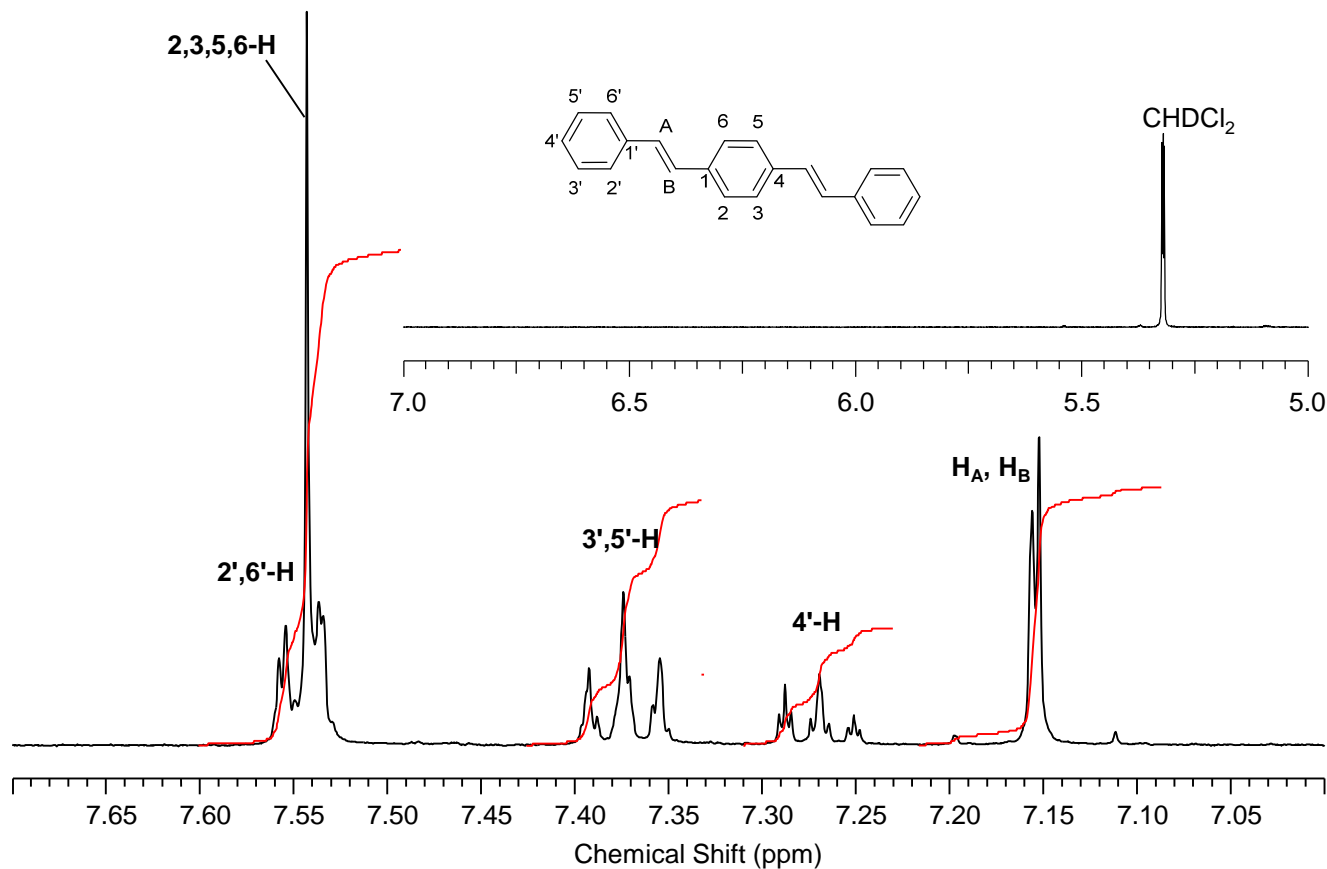


Figure SM 9.2.5.4 – ¹H NMR spectrum (400 MHz, CD₂Cl₂) of the recrystallised *trans,trans*-distyrylbenzene. The inset shows the absence of signals for the *cis*-isomer(s) around δ_H 6.5. CD₂Cl₂ was chosen as the NMR solvent since the residual solvent signal does not overlap with the aromatic/alkene signals; if CDCl₃ is used instead this can cause unnecessary confusion to students.

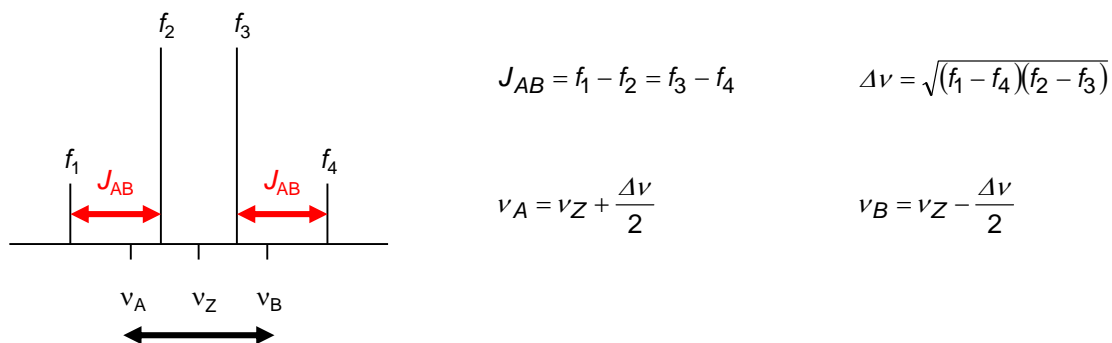


Figure SM 9.2.5.5 – Analysis of an AB spin system. Two spins coupling to only each other will give rise to two doublets. We call them an AX spin system when the signals are far apart, and an AB spin system when they get closer together. An AB system arises when the chemical shift difference in

Hertz $\Delta\nu = \nu_A - \nu_B$ is similar in size to the coupling constant J_{AB} ($\Delta\nu \leq 3 \times J_{AB}$). Spectra of the AB type show two small outer lines (at frequencies f_1 and f_4) and two large inner lines (f_2 and f_3) due to a strongly pronounced roofing effect. In this higher-order spin system, the chemical shift is no longer at the geometric centre of the signal but at the “centre of gravity” between lines 1 and 2 for ν_A , and between lines 3 and 4 for ν_B . The precise chemical shifts need to be calculated.

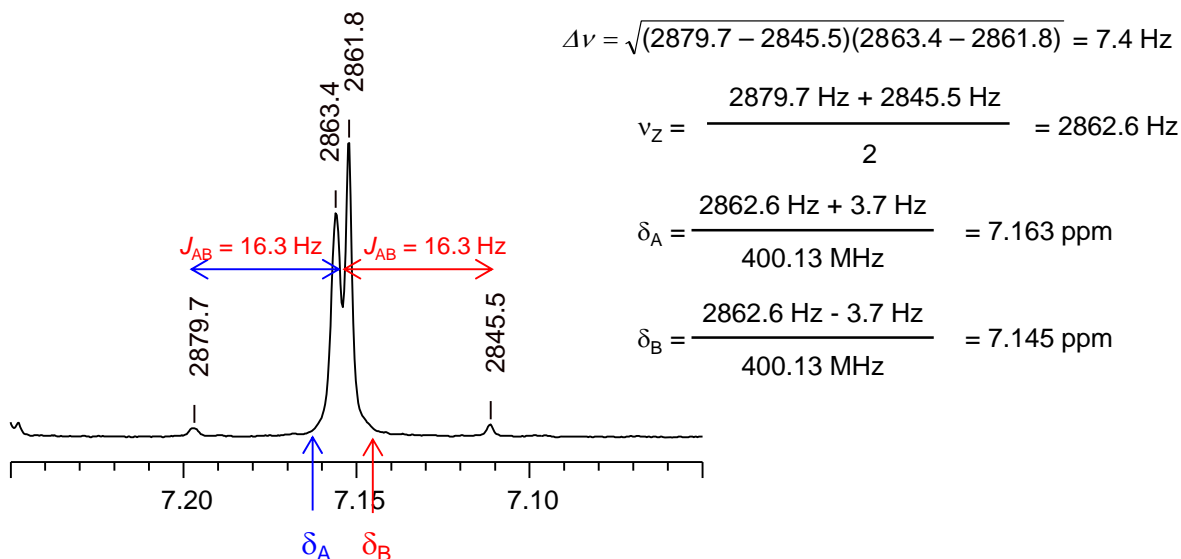


Figure SM 9.2.5.6 – Expansion of alkene signals of the recrystallised *trans,trans*-distyrylbenzene. The two alkene protons are not equivalent and give rise to an AB spin system. The two lines at higher frequency are broadened due to coupling with the aromatic *ortho* protons, but cannot be assigned with certainty without additional 2D NMR evidence (e.g. NOESY). Note: The vicinal coupling constant between the alkene protons is 16.3 Hz, thus confirming the *trans* stereochemistry for the recrystallised product. Some students may come up wrongly with a coupling constant of 1.4 Hz (the difference in Hz between the two inner lines); it is important that students realise that this is an AB spectrum and the outer lines with their low intensity are important.

Table SM 9.2.5.1 – ^1H NMR data for *trans,trans*-distyrylbenzene.

δ_{H}	Integral	Multiplicity	Inferences
7.145	2H	AB	Alkene H ($J_{\text{AB}} = 16.3$ Hz) ^a
7.163	2H	AB	Alkene H ($J_{\text{AB}} = 16.3$ Hz) ^a
7.27	2H	Multiplet ^b	Aromatic H
7.37	4H	Multiplet ^b	Aromatic H
7.53 – 7.56	4H	Multiplet ^c	Aromatic H
7.54	4H	Singlet	Central C_6H_4

a) Without NOESY evidence, these signals cannot be assigned with certainty. **b)** These two signals appear as approximate triplets of triplets and correspond to the *meta* and *para* protons on the peripheral C_6H_5 benzene rings. **c)** This multiplet can be assigned to the *ortho* protons on the peripheral C_6H_5 .

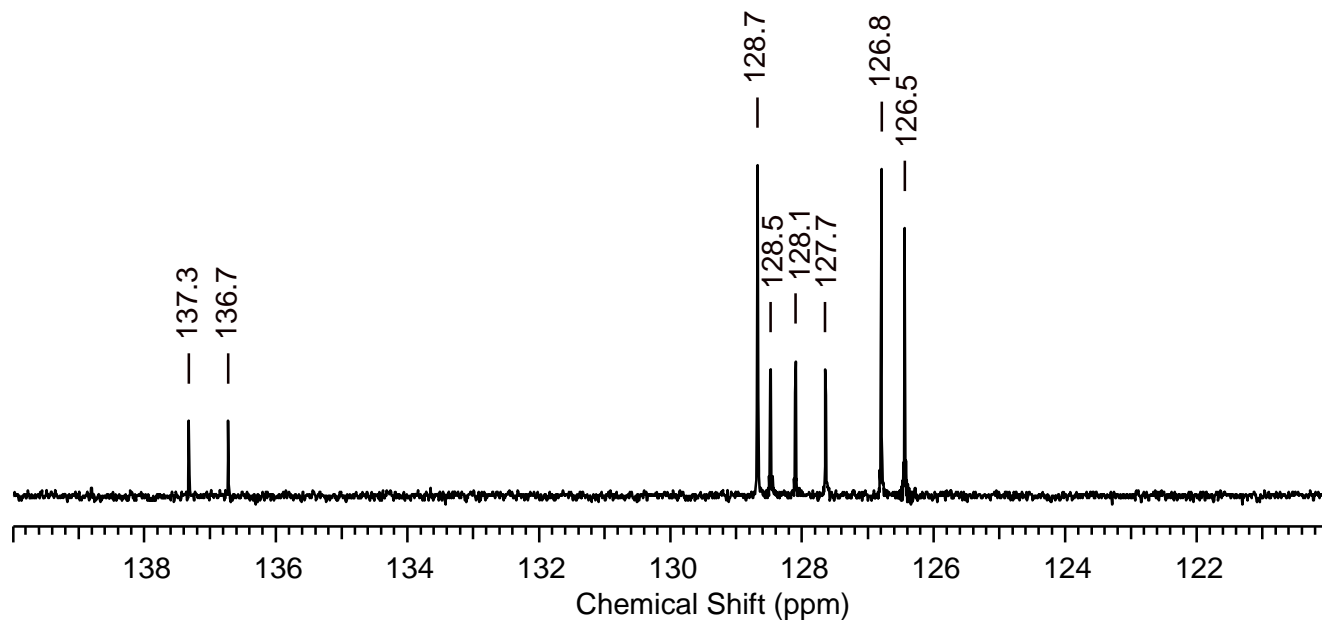


Figure SM 9.2.5.7 – ^{13}C NMR spectrum (100 MHz, CD_2Cl_2) of the recrystallised *trans,trans*-distyrylbenzene. Owing to the symmetry of the product, the ^{13}C NMR spectrum shows only 8 signals.

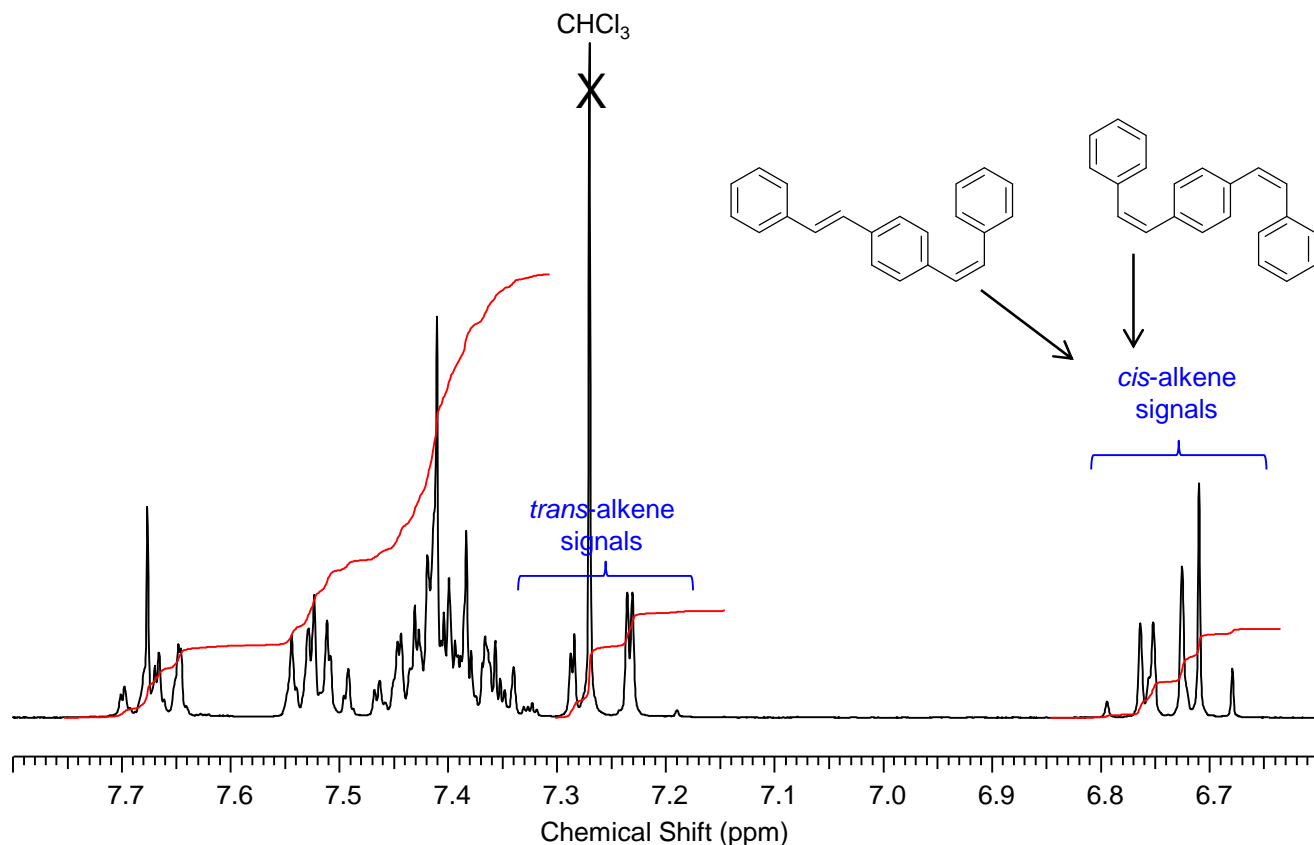


Figure SM 9.2.5.8 – ^1H NMR spectrum (400 MHz, CDCl_3) of the crude distyrylbenzene. The *cis* and *trans* alkene signals can be easily identified by their difference in chemical shift which is δ_{H} 6.7 (for the *cis* alkene protons) and δ_{H} 7.2 (for the *trans* alkene protons and residual CHCl_3). Students should realise that the crude product contains considerable amounts of the *cis,cis* and *cis,trans* isomers (in addition to the *trans,trans* product). The *cis:trans* ratio can be estimated from the integration (ca. 1 : 0.65) of the two signal groups, with *cis* being predominant. Overlap of the residual chloroform signal complicates somewhat the integration analysis; this is the reason why the ^1H NMR spectrum of *trans,trans*-distyrylbenzene in Figure SM 9.2.5.4 was recorded in CD_2Cl_2 .

Conclusions: the *cis* isomer is formed as the major isomer in this Wittig reaction. Iodine is commonly used for converting a *cis-trans* alkene mixture into the thermodynamically more stable *trans* isomer.⁸

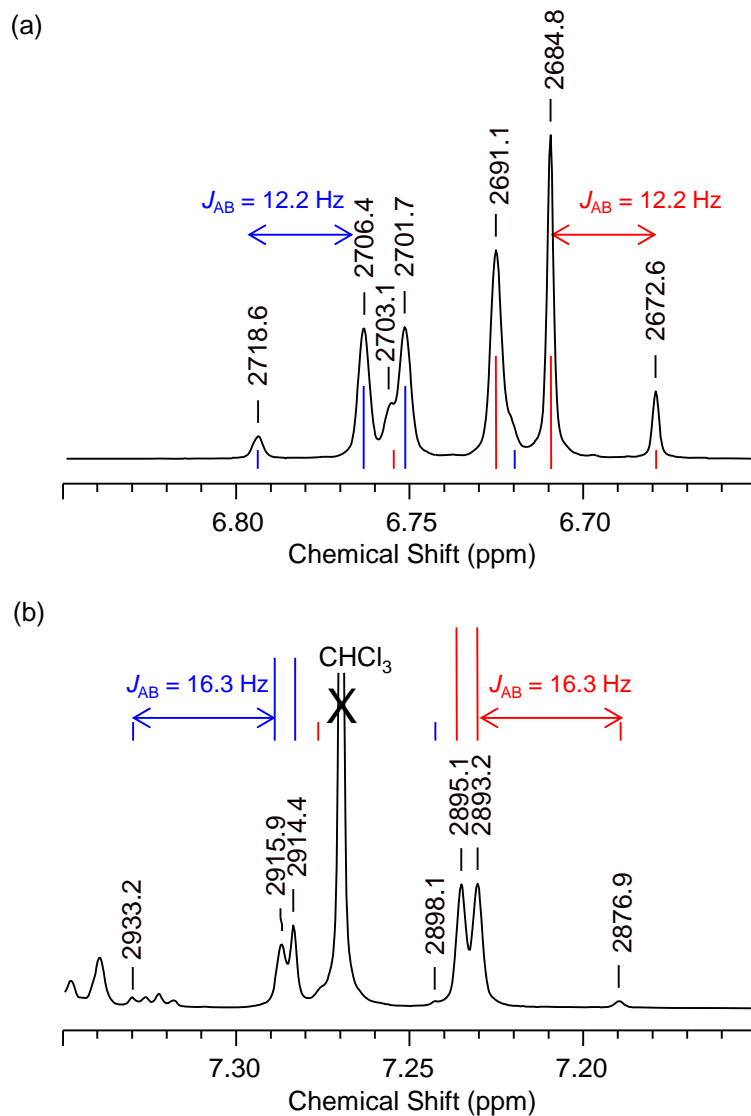


Figure SM 9.2.5.9 – ^1H NMR spectrum (400 MHz, CDCl_3) expansion of (a) the *cis* alkene signals and (b) the *trans* alkene signal region. Closer inspection of the multiplet at δ_{H} 6.7 for the crude product reveals that there are two overlapping AB spectra in the chemical shift region expected for the *cis* isomer, showing two sets of AB spectra with the characteristic 12.2 Hz *cis* coupling.

¹ R. N. McDonald and T. W. Campbell, *Organic Syntheses, Coll. Vol. 5*, 1973, 499.

² J. Gillois, G. Guillermin, M. Savignac, E. Stephan and L. Vo-Quang, *J. Chem. Educ.*, 1980, **57**, 161.

³ E. F. Silversmith, *J. Chem. Educ.*, 1986, **63**, 645.

⁴ C. Jaworek and S. Iacobucci, *J. Chem. Educ.*, 2002, **79**, 111.

⁵ K. C. Nguyen and H. Weizman, *J. Chem. Educ.*, 2007, **84**, 119.

⁶ T. J. Speed, J. P. McIntyre and D. M. Thamattoor, *J. Chem. Educ.*, 2004, **81**, 1355.

⁷ T. W. Campbell and R. N. McDonald, *J. Org. Chem.*, 1959, **24**, 1246.

⁸ S. S. Hepperle, Q. Li and A. L. L. East, *J. Phys. Chem. A*, 2005, **109**, 10975.

Synthesis and Reactivity of Phosphorus Ylides

Supplementary Material

Experiment Notes	1
Characterization Data	
Compounds 5 , 7 and 8	3
Figures	
¹ H and ¹³ C NMR spectra	4
³¹ P spectrum.....	10

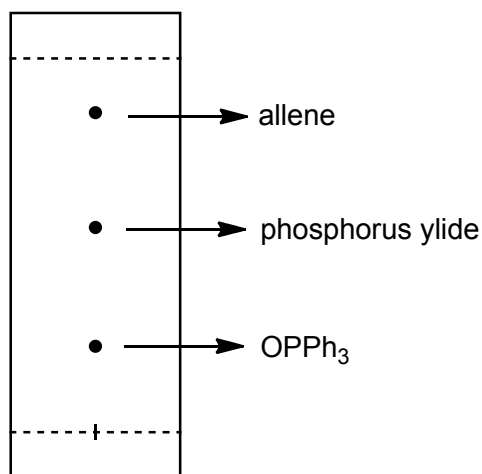
The main goal of this experiment is to illustrate the use of the Wittig reaction as a synthetic tool for the preparation of different compounds starting from simple phosphorus ylides. In these experiments one aspect that should be emphasized is the experimental simplicity of these reactions in the preparation of moderately complex molecules resulting from the formation of new carbon-carbon double bonds.

The student body is of advanced organic chemistry, in which the concepts of ylides formation and Wittig reactions were taught. The students should be skilled enough to perform the isolation of the products, as in here described.

Additional notes for the preparation of ethyl 2-(triphenylphosphoranylidene)acetate (3a) and benzyl 2-(triphenylphosphoranylidene)acetate (3b): This procedure allows the preparation of the products in yields ranging from 70% to 85% when performed by five undergraduate students. The monitoring of the reaction progress is easily accomplished since the phosphonium salt is insoluble in toluene, allowing the students to observe the formation of a white precipitate in the reaction mixture. Some special concern is needed for the neutralization of the phosphonium salt. The instructor should control the neutralization reaction time, to not exceed 30 minutes, preventing in this way the formation of hydrolysis products. Due the difficulty in properly drying the products in a vacuum pump in a short time, it is suggested that the students dissolve the ylides in dichloromethane and use a drying agent such as anhydrous sodium sulphate after the final filtration step.

Ethyl 2-(triphenylphosphoranylidene)acetate (**3a**) is obtained as a white solid (lit. mp 116-117 °C)¹ and can be stored at room temperature until the next lab session. Benzyl 2-(triphenylphosphoranylidene)acetate (**3b**) is obtained as a white solid (lit. mp 120-122 °C)² and should be stored in the refrigerator until the next lab session.

Additional notes for the preparation of benzyl penta-2,3-dienoate (7): This procedure allows the preparation of the product in yields ranging from 55% to 66% when performed by four undergraduate students. The monitoring of the reaction by TLC is easy due to the different R_f values of the products, as observed for a silica TLC eluted with AcOEt/ *n*-hexane (1:1) after sample dilution with CH_2Cl_2 (Figure **SM 9.2.6.1**). The precipitation of the triethylamine salt in the reaction mixture can also be observed by the students. The isolation of the allene is accomplished by column chromatography using AcOEt/ *n*-hexane (1:2) as eluent and silica as the stationary phase. At this point, the instructor should check if the column is properly set up: with the sand, the silica gel and the cotton not too compacted. (Figure **SM 9.2.6.2**).



Eluent: AcOEt/ *n*-hexane (1:1)

Figure SM 9.2.6.1- TLC of the reaction mixture.

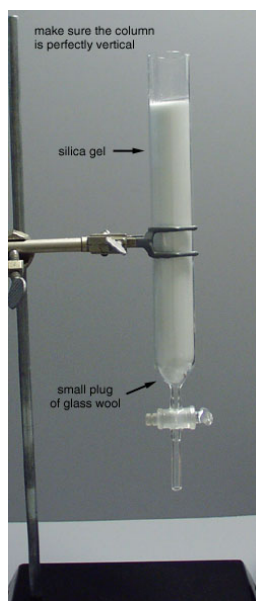
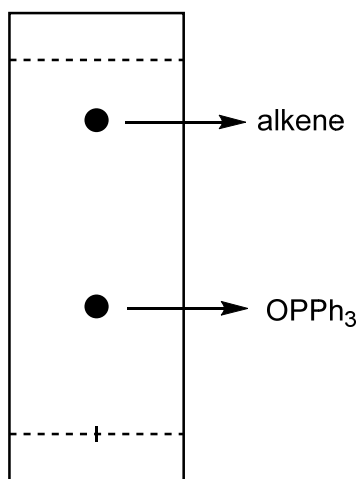


Figure SM 9.2.6.2- Column chromatography apparatus.

Additional notes for the preparation of diethyl 2-chloro-3-methoxybutenedioate (8): This procedure allows the preparation of the product in yields around 65% when performed by experienced researchers and in 50-60% range when executed by undergraduate students. The reaction is very fast and, as the previous reaction, can be easily monitored by TLC due to the different R_f values of the products, as observed for a silica TLC eluted with AcOEt/ *n*-hexane (2:1) after sample dilution with CH_2Cl_2 (Figure **SM 9.2.6.3**). The reaction crude can be stored in the refrigerator after work-up and be purified in an extra class. The alkene is purified by column chromatography using AcOEt/*n*-hexane (2:1) as eluent and silica as the stationary phase and, as in the previous example, the instructor should at this stage check if the column is properly set up (Figure **SM 9.2.6.2**).



Eluent: AcOEt/ *n*-hexane (2:1)

Figure SM 9.2.6.3 TLC of the reaction mixture.

Characterization Data

Diethyl 2-oxo-3-triphenylphosphoranylidenebutanedioate (**5**)

Ylide **5** was obtained as a white solid in 76% yield. mp 136-138 °C; IR (KBr) ν_{max} = 1736, 1726, 1674, 1543 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ = 7.72- 7.67 (m, ArH, 6H), 7.58-7.56 (m, ArH, 3H), 7.51-7.47 (m, ArH, 6H), 4.27 (q, J = 7.2 Hz, 2H), 3.83 (q, J = 7.2 Hz, 2H), 1.36 (t, J = 7.2 Hz, 3H), 0.77 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ = 184.7 (d, $^2J_{\text{CP}}$ = 6.2 Hz), 167.5 (d, $^3J_{\text{CP}}$ = 14.7 Hz), 167.2 (d,

$^3J_{CP} = 12.9$ Hz), 133.7, 133.6, 132.5, 132.4, 128.8, 128.7, 124.7, 123.8, 67.6 (d, $^1J_{CP} = 110$ Hz), 61.0, 59.1, 14.2, 13.8.

Benzyl penta-2,3-dienoate (**7**)

Allene **7** was obtained as colorless oil in 66% yield. IR (film) $\nu_{\max} = 1721$ and 1964 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) $\delta = 7.36$ - 7.35 (m, ArH, 5H), 5.62- 5.60 (m, 2H), 5.18 (s, 2H), 1.78 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 213.3$, 166.0, 136.1, 128.6, 128.5, 128.3, 128.1, 90.4, 87.5, 66.4, 12.7.

Diethyl 2-chloro-3-methoxybutenedioate (**8**)

Alkene **8** was isolated as colorless oil in 61% yield. IR (film) $\nu_{\max} = 2986$, 1740, 1610 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) $\delta = 4.36$ and 4.24 (each q, 2H, CH_3CH_2), 3.88 (s, 3H), 1.38 and 1.31 (each t, 3H, CH_3CH_2); ^{13}C δ (100 MHz) 162.6, 161.7, 155.7, 105.8, 62.6, 62.0, 59.8, 58.1, 14.0, 13.8; MS (CI) m/z (%) = 254 [M (^{35}Cl)+ NH_4] $^+$ (100); HRMS (CI): calcd. $\text{C}_9\text{H}_{13}^{35}\text{ClO}_5$ [M] $^+$ 236.045, found 236.045.

^1H and ^{13}C NMR spectra

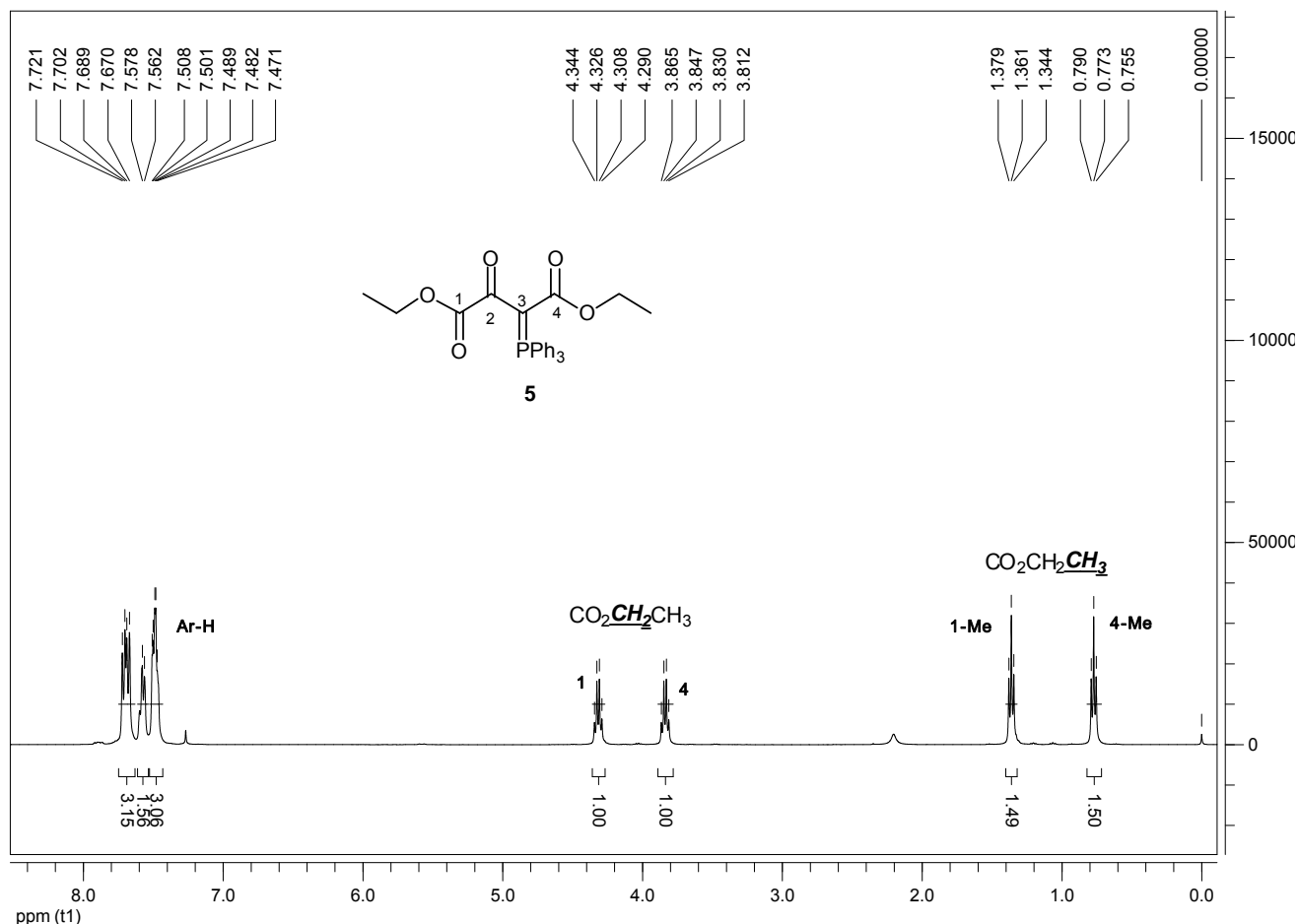


Figure SM 9.2.6.4- ^1H NMR spectrum (400 MHz, CDCl_3) of compound **5**.

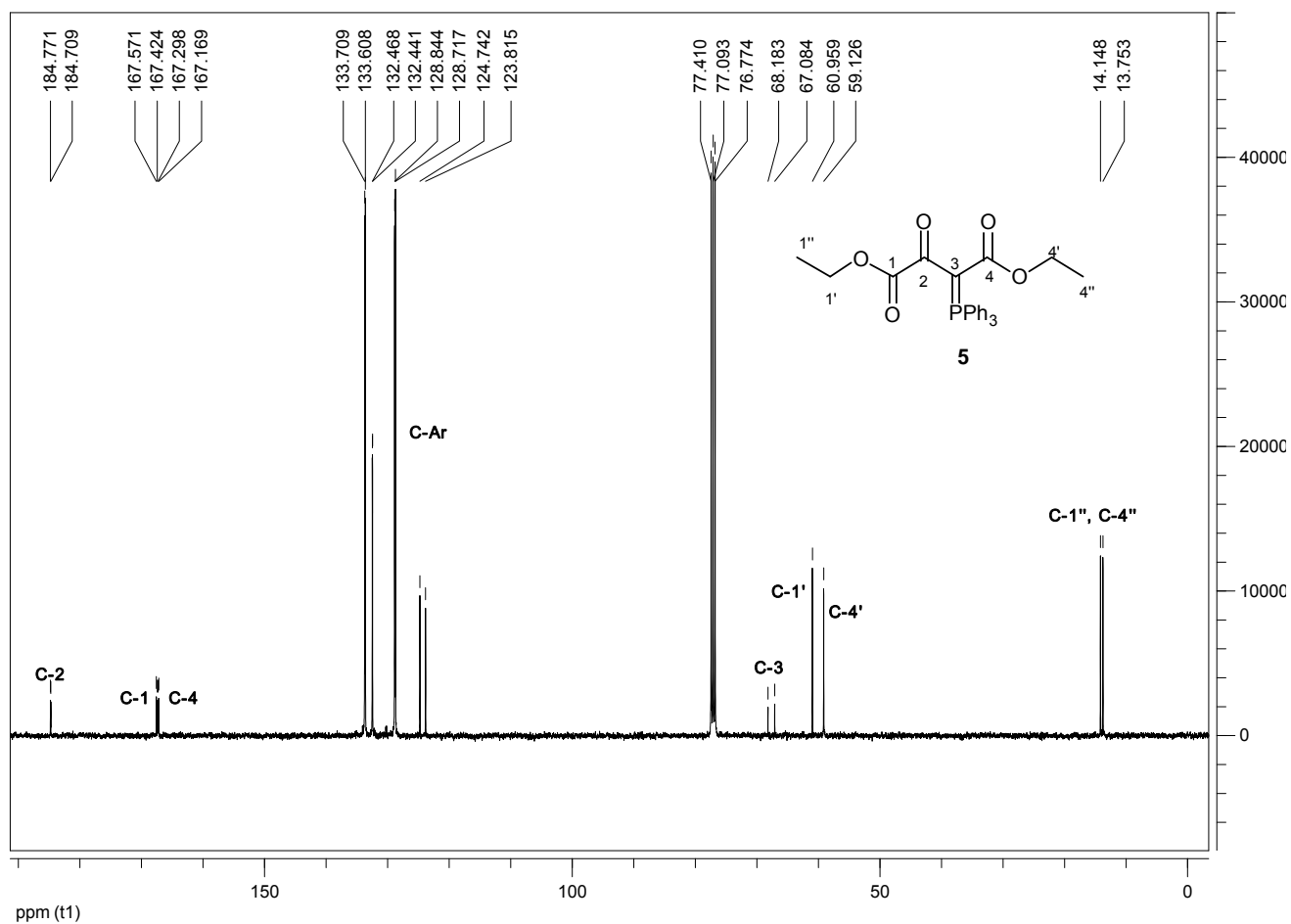


Figure SM 9.2.6.5- ^{13}C NMR spectrum (100 MHz, CDCl_3) of compound **5**.

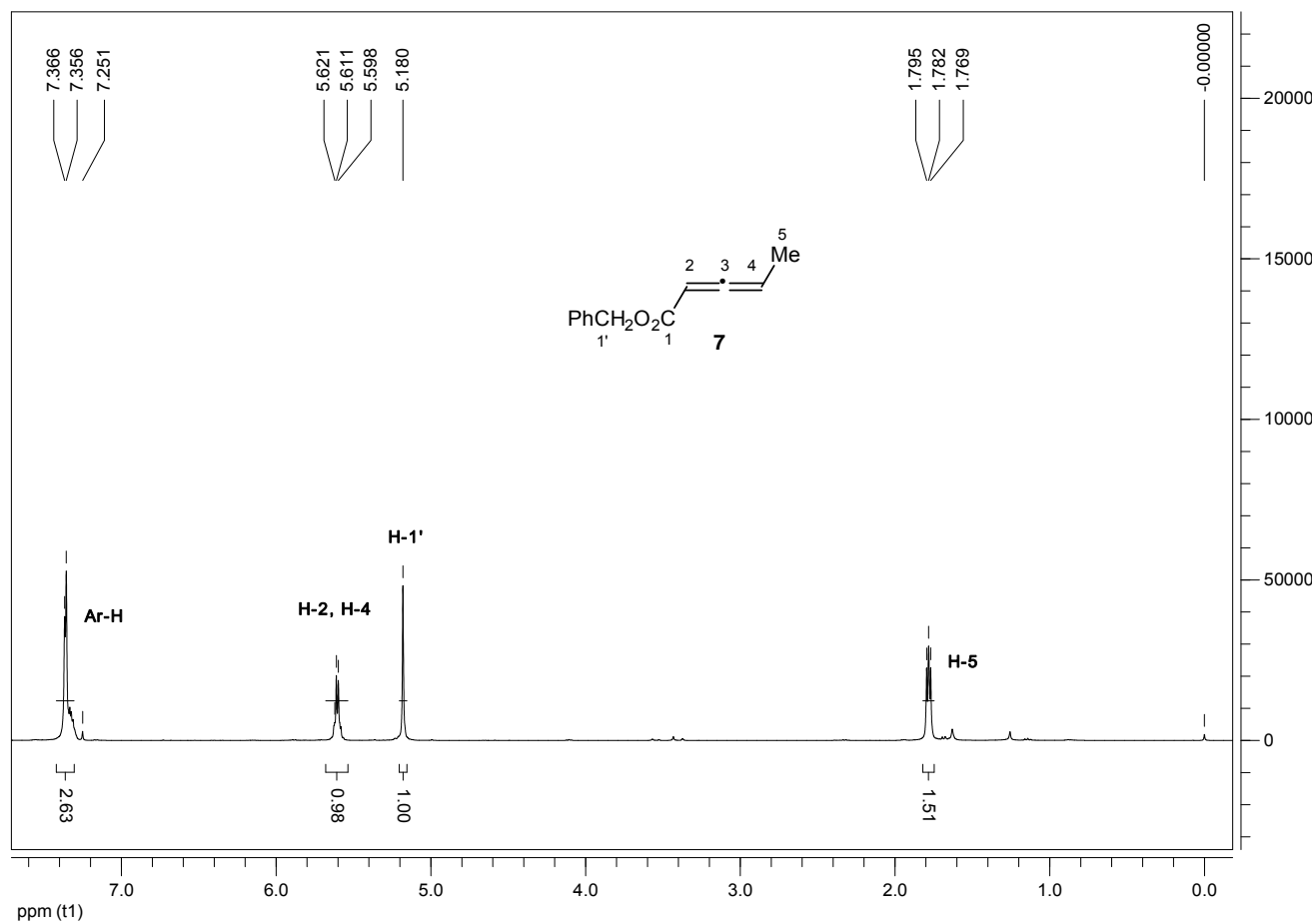


Figure SM 9.2.6.6- ¹H NMR spectrum (400 MHz, CDCl₃) of compound 7.

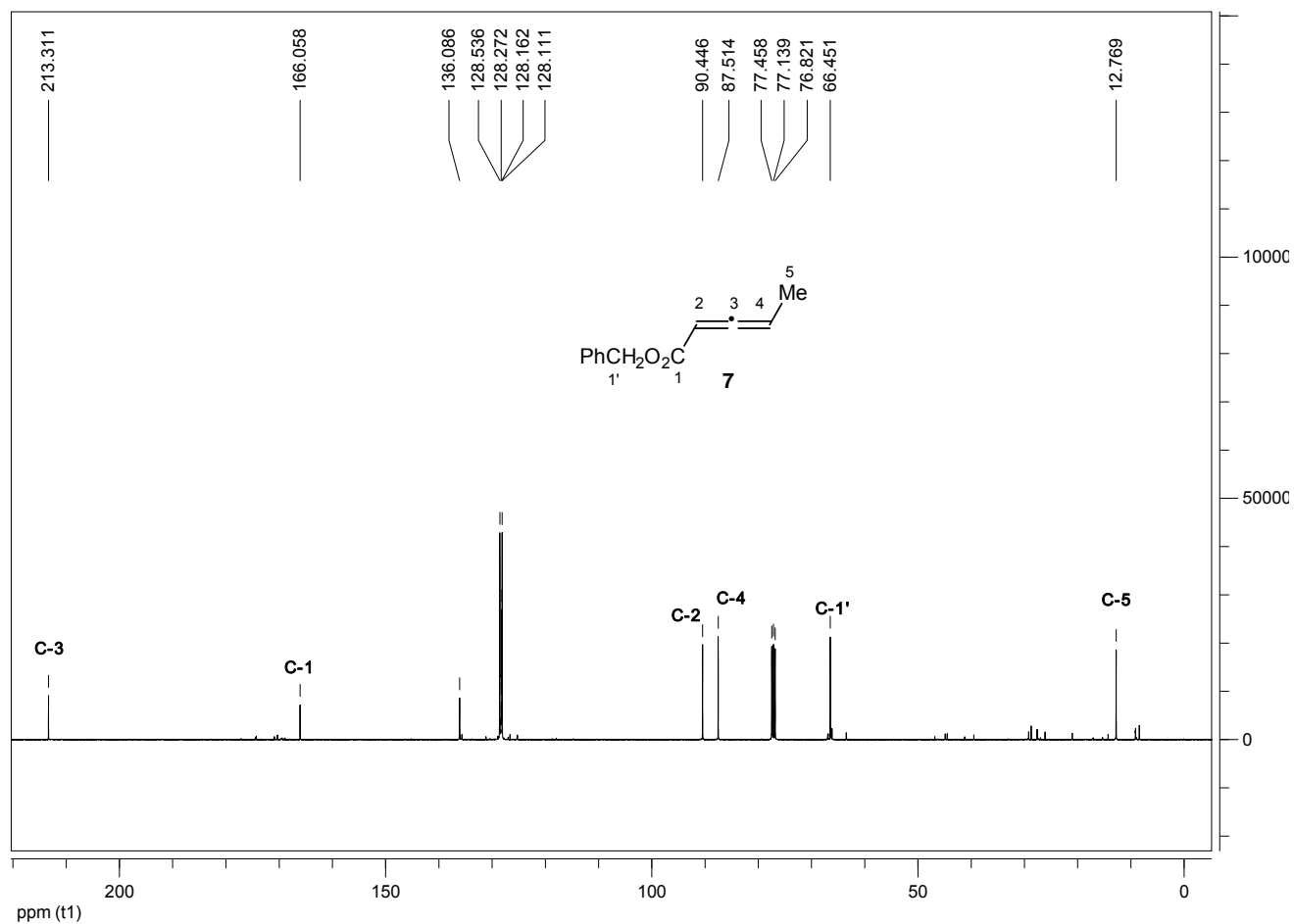


Figure SM 9.2.6.7- ^{13}C NMR spectrum (100 MHz, CDCl_3) of compound 7.

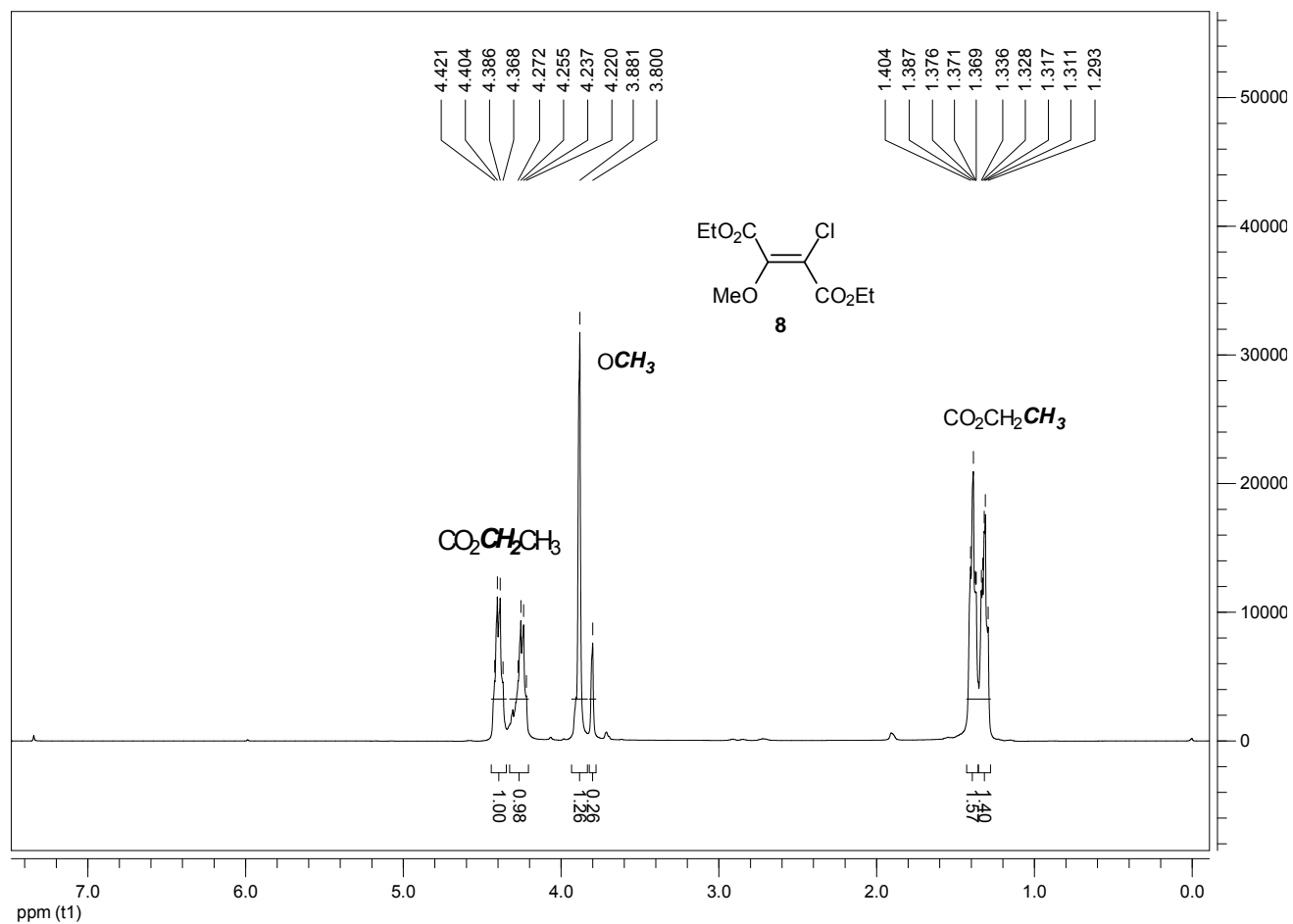


Figure SM 9.2.6.8- ^1H NMR spectrum (400 MHz, CDCl_3) of compound **8**.

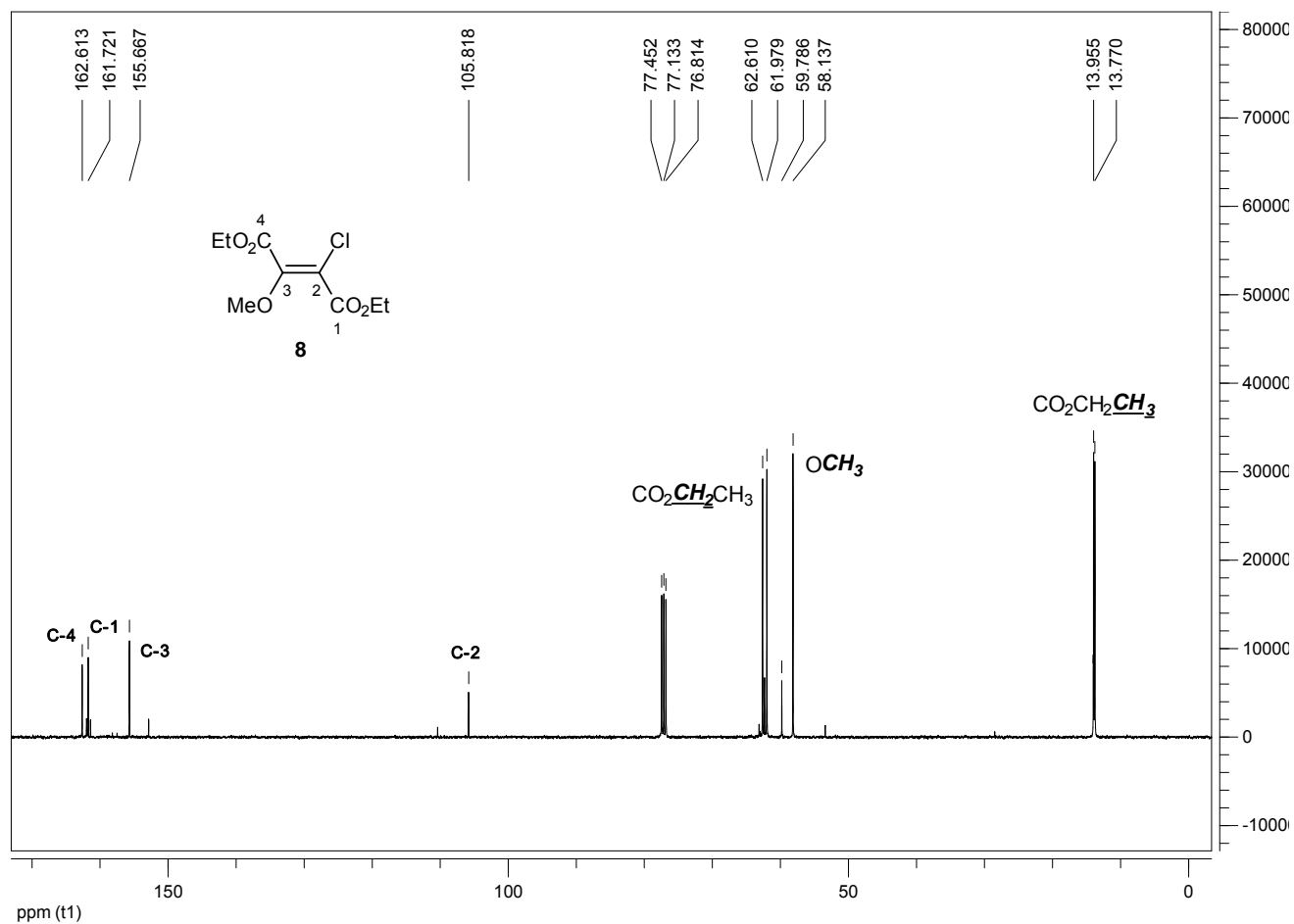


Figure SM 9.2.6.9- ^{13}C NMR spectrum (100 MHz, CDCl_3) of compound **8**.

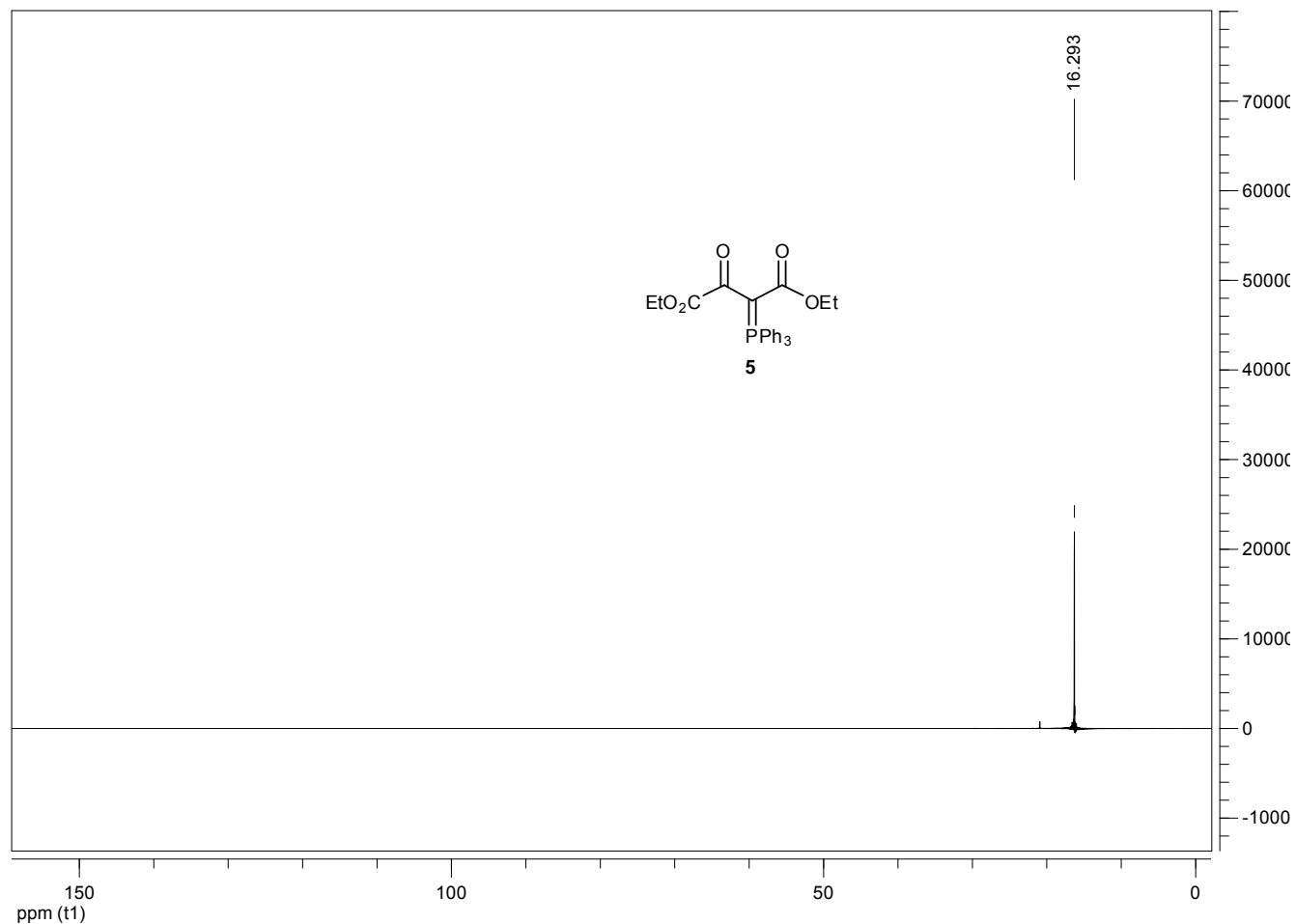


Figure SM 9.2.6.10- ^{31}P NMR spectrum (161.7 MHz, CDCl_3) of compound **5**.

- ¹ O. Isler, H. Gutmann, M. Montanon, R. Ruegg, G. Ryser, and P. Zeller, *Helv. Chem. Acta*, 1957, **40**, 1242.
² M. P. Jr. Cook, and D. L. Burman, *J. Org. Chem.*, 1982, **47**, 4955.

Synthesis of 4-(Thiophen-2-yl)pyrrolidin-2-one via Horner-Wadsworth-

Emmons reaction and reductive cyclisation

Supporting Information

This experiment is designed as a series of 4 sequential steps to introduce third year undergraduate students to multi-step organic synthesis. In addition, the experiment exposes the student cohort to a plethora of practical (handling pyrophoric reagents, vacuum distillation, recrystallisation, utilising dry solvents, column chromatography) and theoretical (planning experimental quantities, time management) skills, which they will utilise going forward to their 4th year studies or take away into industry. Below are highlighted additional comments for each synthetic step along with the associated spectrum of the product.

Additional information for Step 1

This step is very straightforward and gives quantitative yields. The reaction cannot be followed easily by TLC, hence the introduction of monitoring by GC-MS. Leaving the reaction for prolonged periods of time increases the quantity of a decarboxylative by-product, which can be observed in the NMR. This product can be stored and kept for many weeks without loss of purity.

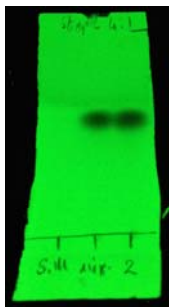
Signals for decarboxylation product: δ_{H} (400MHz; CDCl_3) 1.26-1.33 (3H, m, CH_3), 3.53-3.57 (6H, m, $\text{P}(\text{OCH}_3)_2$).

Additional information for Step 2

It is important to use freshly distilled thiophene as this compound is hygroscopic. Clearly not removing sufficient THF in the work-up will result in lower yields. Yields of ca. 60% may be expected. Whilst thiophene aldehyde can be stored, in our experience it is better to be used within a couple of weeks. If to be left longer than that, this product is commercially available and can be given to students on production of their original ^1H NMR for their synthetic product.

b.p. 80 - 82 °C/ 13 mmHg (lit. 75-77 °C /11 mmHg, 198 °C/760 mmHg).

TLC (*n*-hexane/EtOAc 4:1), visualised under UV



From left to right (thiophene, mixture of the two spots, product 2)

Additional information for Step 3

Yields of 70% or more are achievable. As the product is slightly volatile, care with rotary evaporation needs to be taken. Purification by column chromatography is very quick and straightforward. This product can be stored at this point and used at a later date.

TLC (*n*-hexane/EtOAc 4:1), visualised under UV

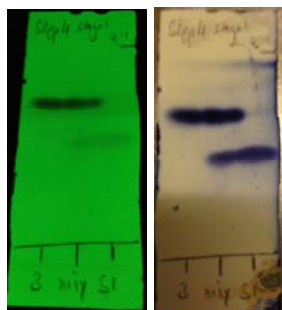


From left to right (product 2, mixture of the two spots, product 3)

Additional information for Step 4

Stage 1: As the nitromethane addition product is slightly volatile, care with rotary evaporation needs to be taken. Yields of 60-70% are achievable. Monitoring the reaction by TLC is easy as is product purification by column chromatography.

TLC (*n*-hexane/EtOAc 4:1), visualised under UV and with PMA/Ce(SO₄)₂

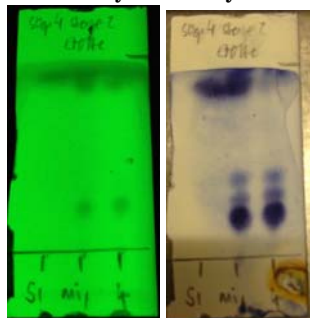


From left to right (product 3, mixture of the two spots, intermediate nitro product)

Stage 2: Following this procedure, yields of 60-80% are achievable. Monitoring the reaction by TLC is easy as is product purification by column chromatography (simply a filtration). There are some minor impurities, which cannot be removed.

mp. 84 - 85°C (lit. 89 °C, from diisopropyl ether)

TLC (EtOAc), visualised under UV and with PMA/Ce(SO₄)₂



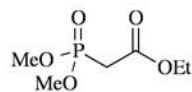
From left to right (intermediate nitro product, mixture of the two spots, product

4)

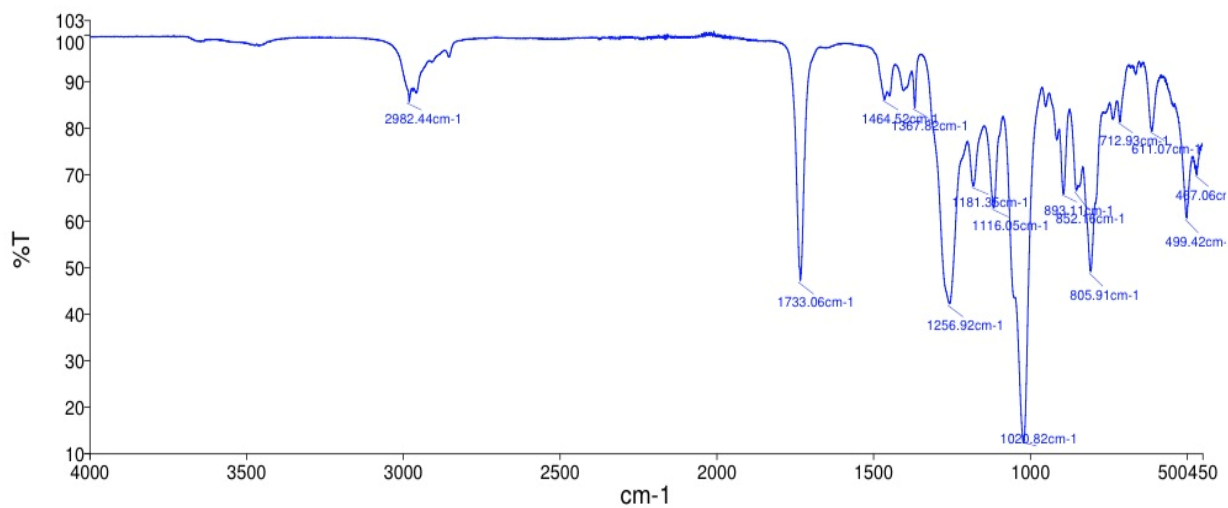
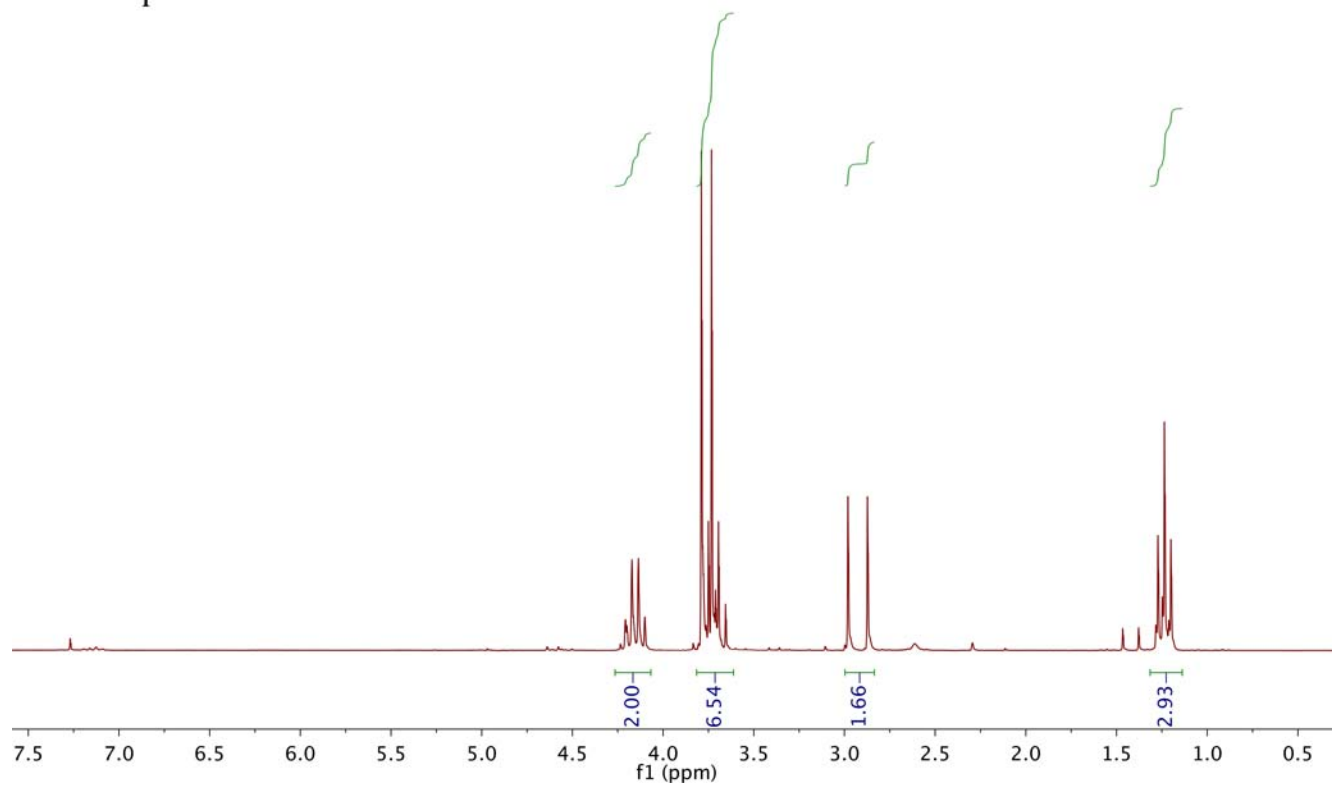
Spectra

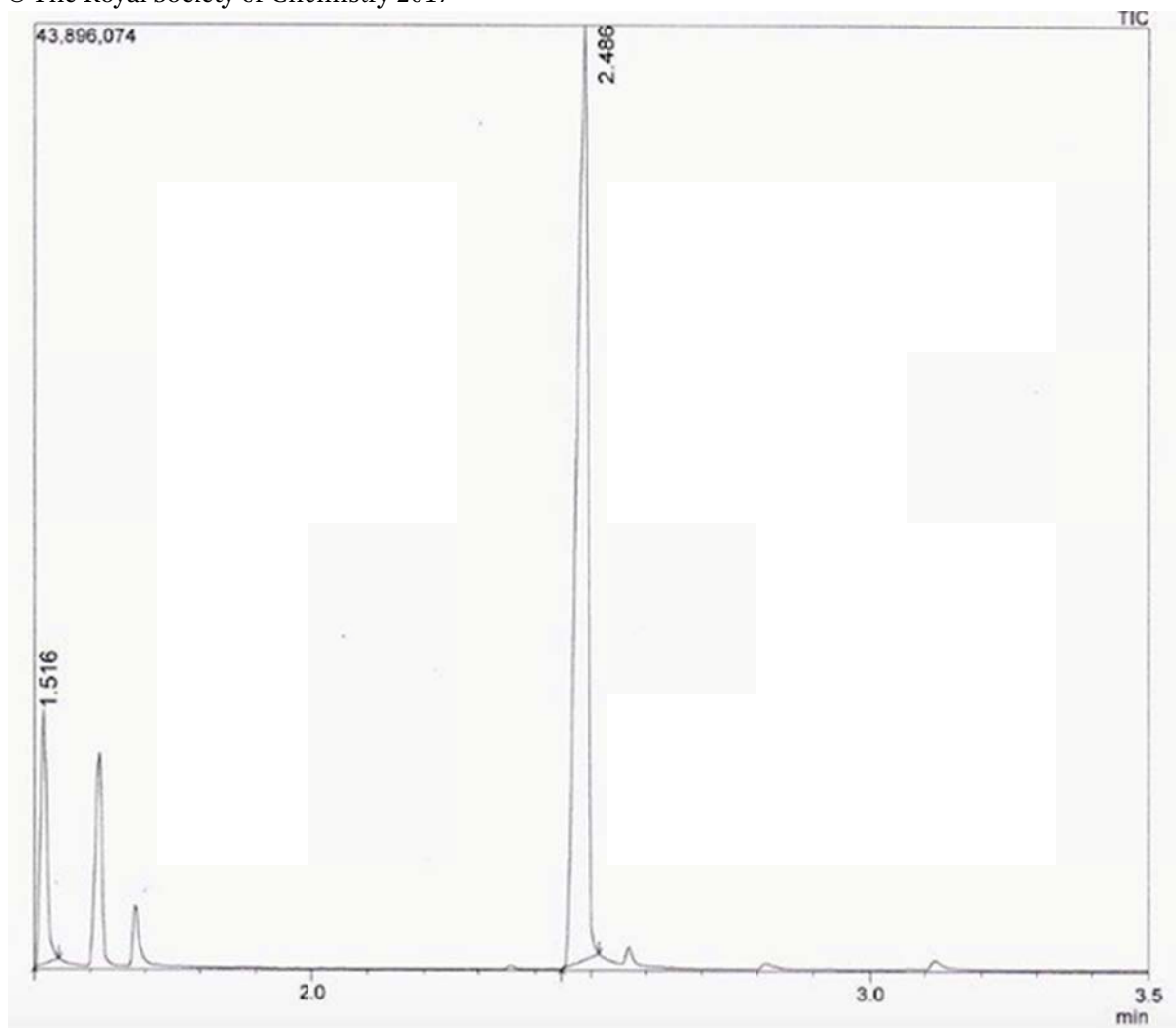
Step 1 (¹H NMR, IR and GCMS)

Ethyl 2-(dimethoxyphosphoryl)acetate (1)



1



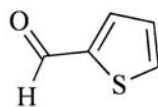


Conditions

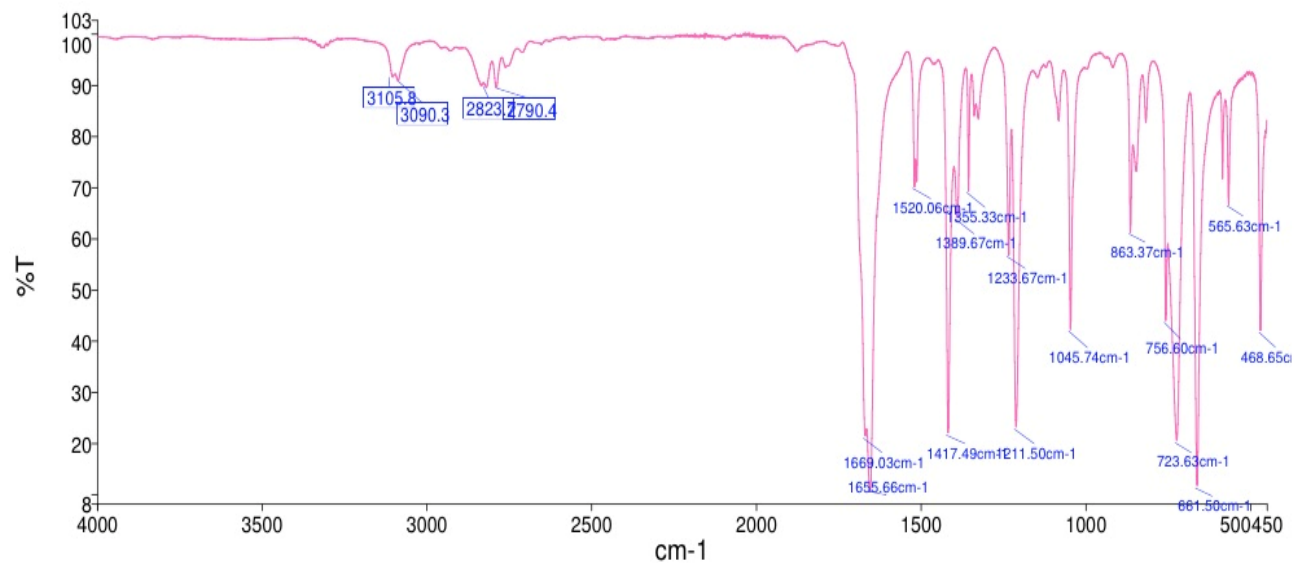
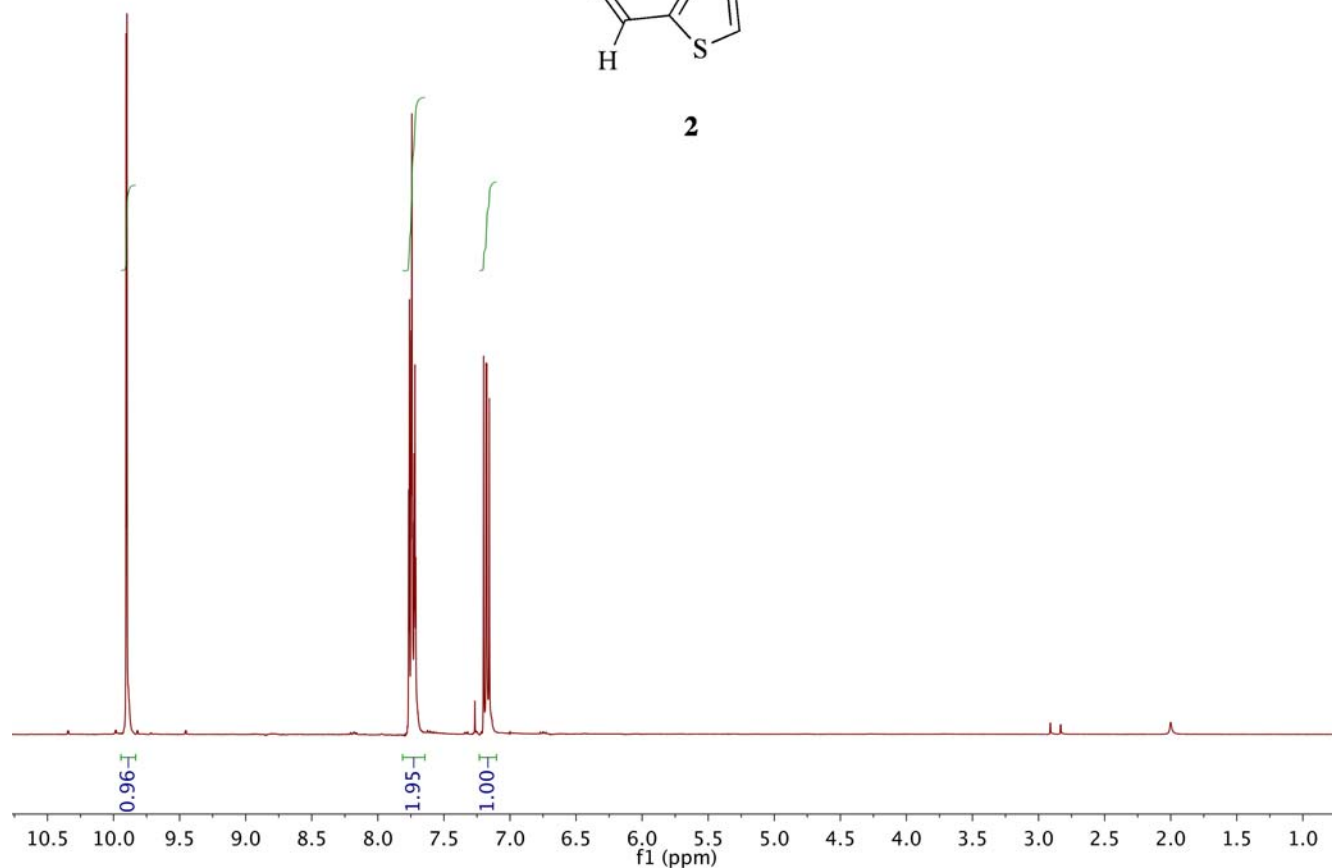
Shimadzu QP2010-Ultra, EI is carried at 70eV and the working mass range is 35 – 650 u. The column is a Rxi-5Sil MS (0.15 μ m x 10m x 0.15 mm) ran with Helium at 0.41 mL/min with a method comprising 50 °C for 1 min (hold) then ramp to 250 °C with a rate of 120 °C/min and hold at 250 °C for 1 min.

Step 2 (¹H NMR, IR)

Thiophene-2-carbaldehyde (2)

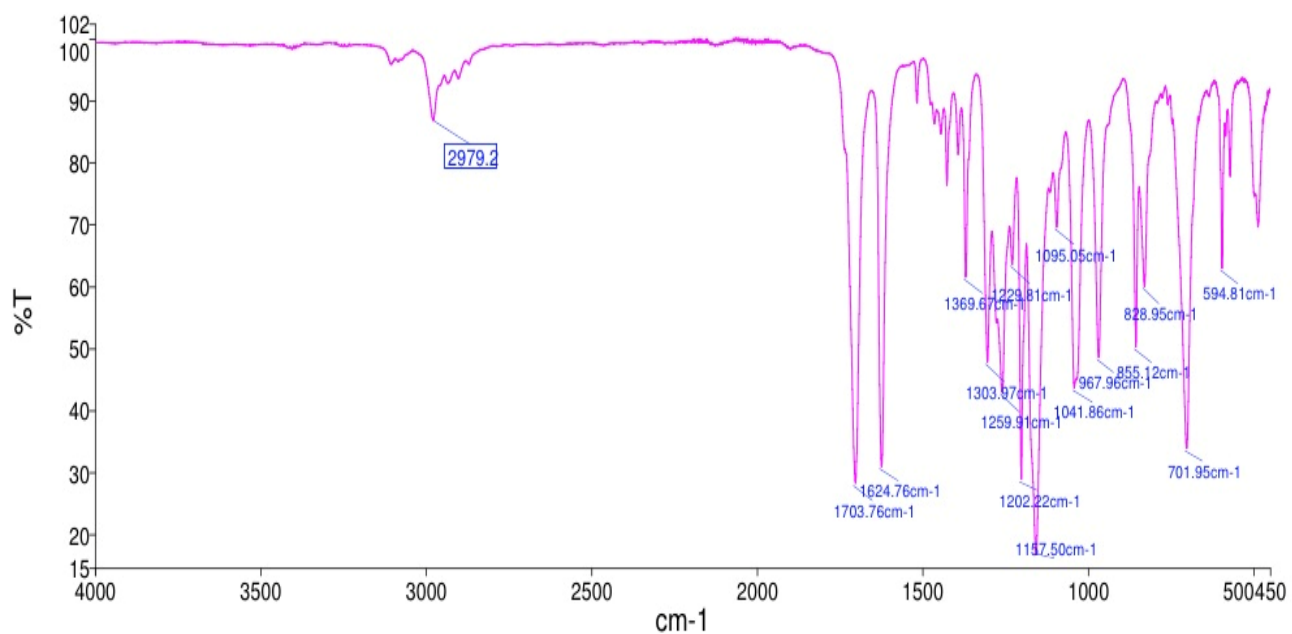
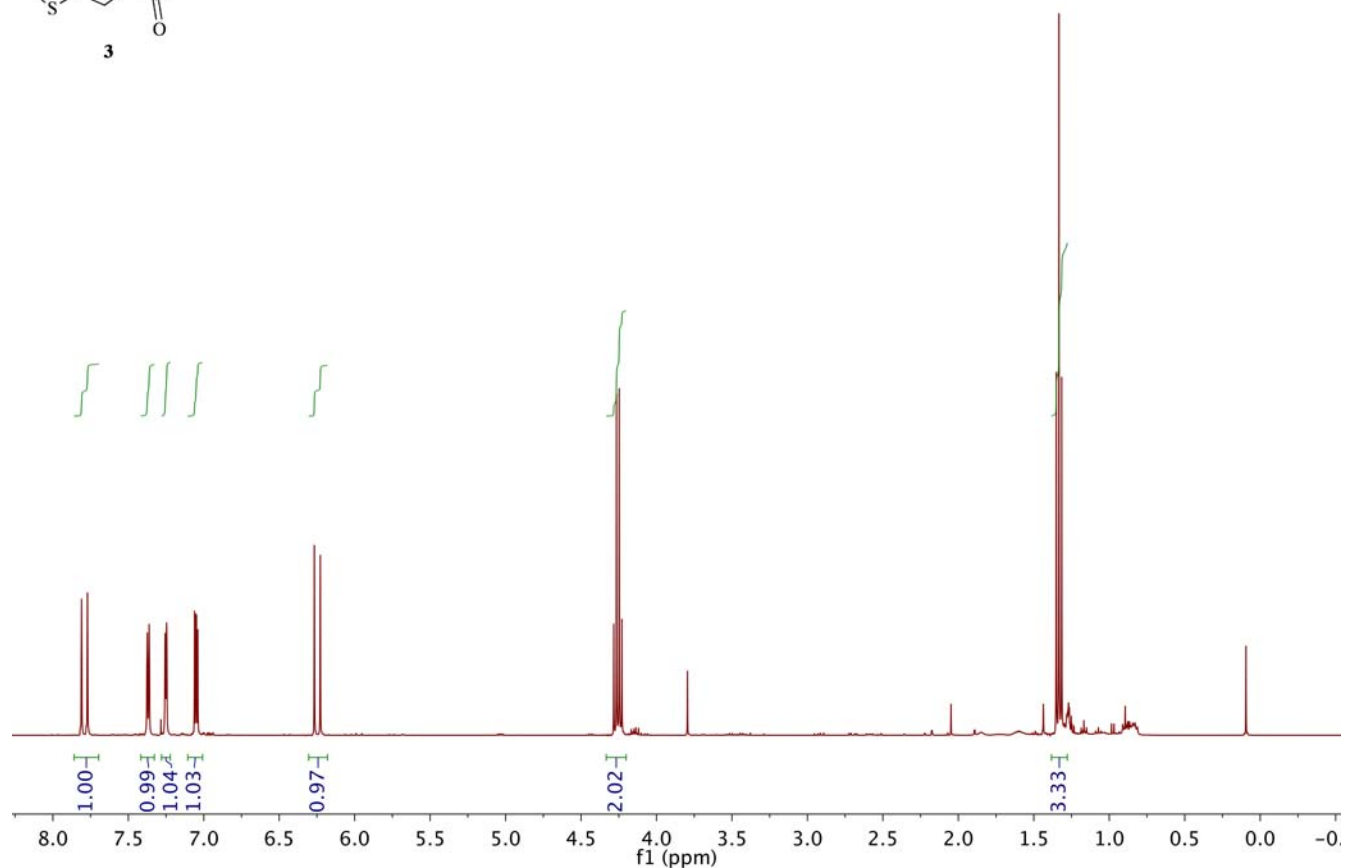
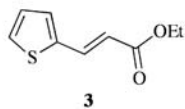


2



Step 3 (¹H NMR, IR)

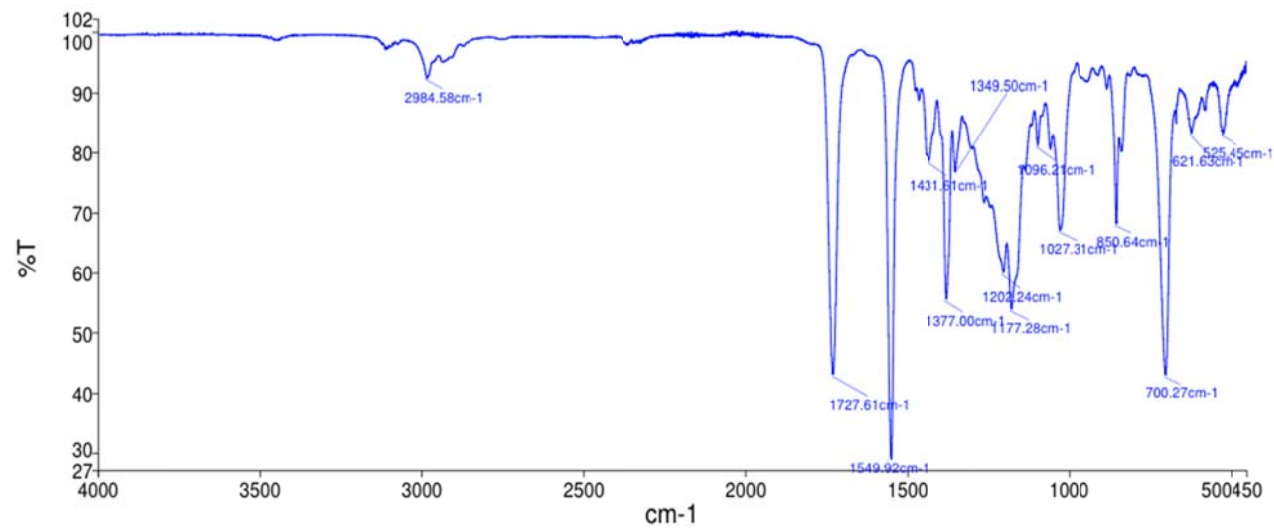
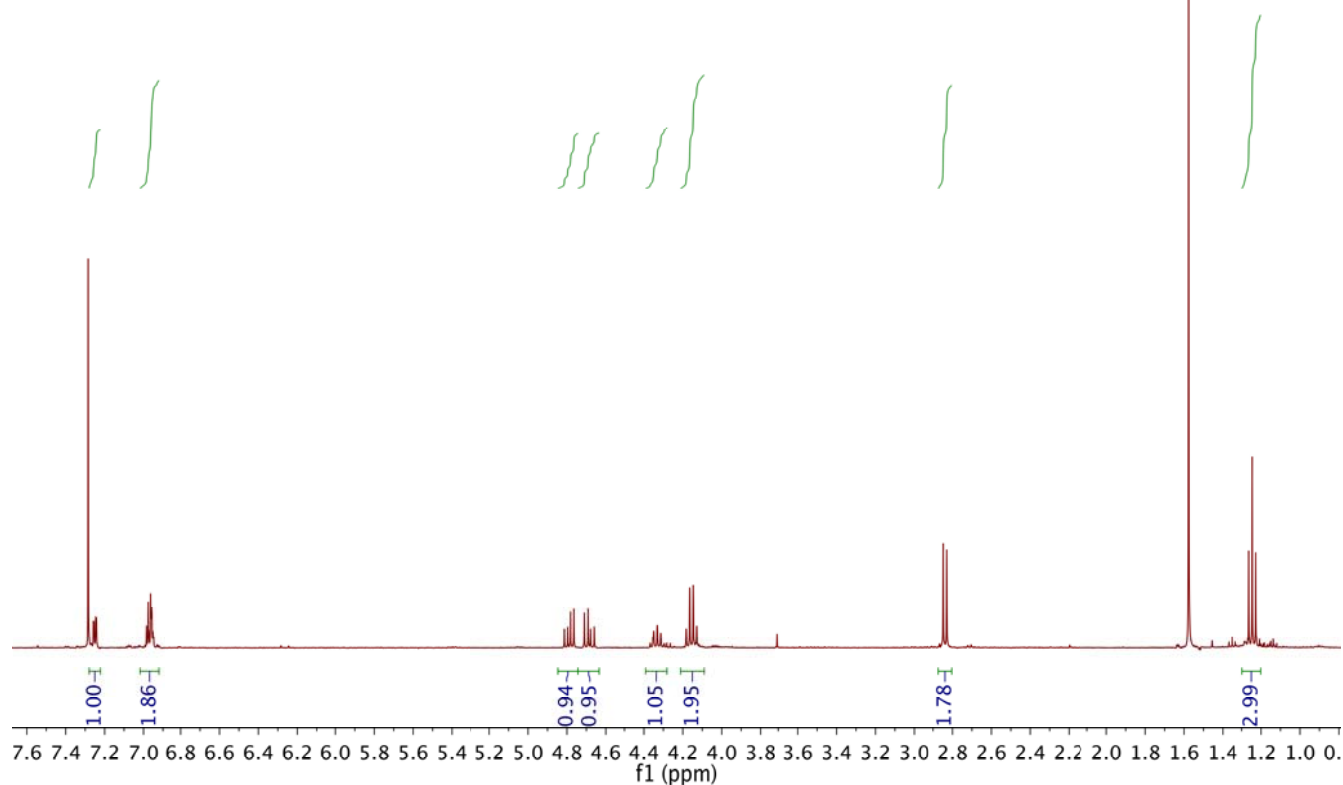
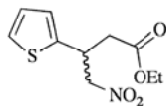
Ethyl (2E)-3-(thiophen-2-yl)prop-2-enoate (3)



Step 4 (¹H NMR, IR)

4-(Thiophen-2-yl)pyrrolidin-2-one (4)

Stage One



Stage Two

