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## The Aldol Condensation



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## Objectives

The objective of this experiment is to understand aspects of carbonyl chemistry and carbon-carbon bond formations using the well-known aldol condensation reaction. Reaction products formed in this experiment will be primarily characterized by  $^1\text{H}$  NMR spectroscopy using the Spinsolve benchtop NMR spectrometer.

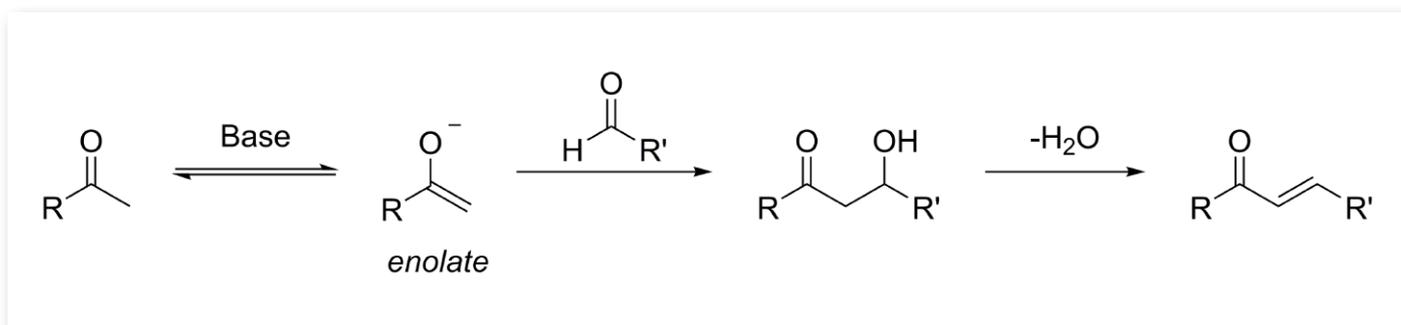
## Introduction

Carbon-carbon bond formation is one of the cornerstones of organic synthesis. One of the key reactions used, the aldol condensation, features the reaction of two carbonyl compounds to form a new  $\alpha$ -hydroxy carbonyl compound.<sup>1</sup> This reaction can be performed under acid- or base-catalyzed conditions, and usually results in the formation of an  $\alpha,\beta$ -unsaturated carbonyl compound. The general base-catalysed reaction is shown in Scheme 1. One of the reacting species must contain a protonated  $\alpha$ -carbon adjacent to the carbonyl centre. The proton attached to this carbon is acidic enough to be abstracted by base to form an *enolate* species. Upon reaction with a second carbonyl compound, the  $\alpha$ -hydroxy carbonyl compound is formed, which can undergo E1cB elimination of water to form an *E*-alkene.

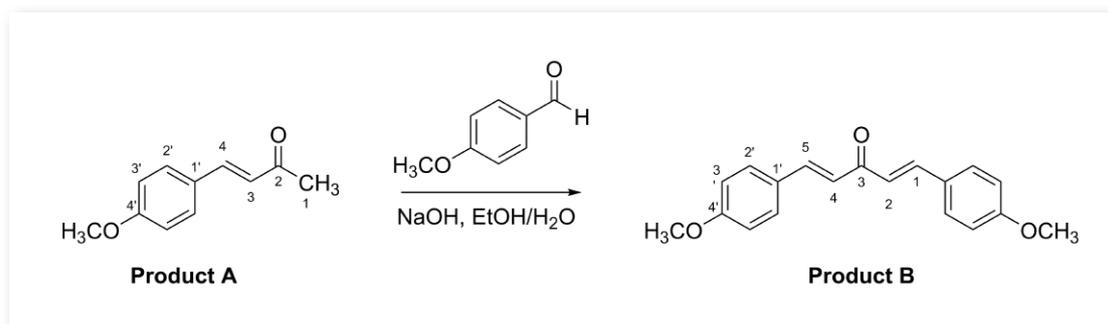
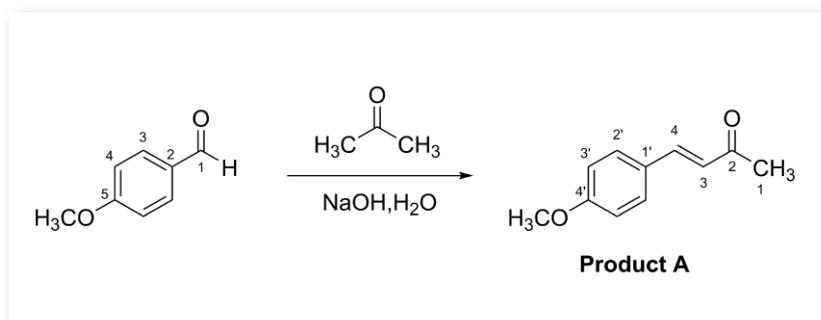
In this experiment, the aldol condensation of acetone and *p*-anisaldehyde (4-methoxybenzaldehyde) is carried out under basic conditions (Scheme 2). By employing a stepwise sequence, you will be able to isolate the mono-addition (Product A), and repeat the reaction, this time using (Product A) as the source ketone to form the bis-addition (Product B).

## Safety

This experiment must be performed in a fume hood with adequate ventilation. Acetophenone and benzaldehyde are harmful – handle with care. Potassium hydroxide is caustic and corrosive – use with caution. Wear appropriate safety equipment before commencing with this experiment. Consult the relevant MSDS for additional safety information.



Scheme 1. Base-catalyzed aldol condensation reaction.



Scheme 2. Synthetic two-step preparation of aldol products from acetone and *p*-anisaldehyde.

### Preparation of 4-(4'-methoxyphenyl)-3-buten-2-one (Product A)

In a 100 mL round bottom flask prepare a solution of *p*-anisaldehyde (1.2 mL, 10 mmol) in acetone (15 mL), add a magnetic flea and clamp the flask above a magnetic stirrer. In a separate beaker, prepare a solution of potassium hydroxide (1.0 g) in water (20 mL) and add slowly (over 2 minutes) to the mixture in the round bottom flask while stirring. Stir the solution for 20 minutes and add approximately 40 mL of water to the reaction mixture to ensure that all the product has precipitated. Filter the resulting solid by vacuum filtration and wash with water. Dry the solid and recrystallize from ethanol (Figure 1).



Figure 1. Recrystallized 4-(4'-methoxyphenyl)but-3-en-2-one (Product A).

## NMR Spectra

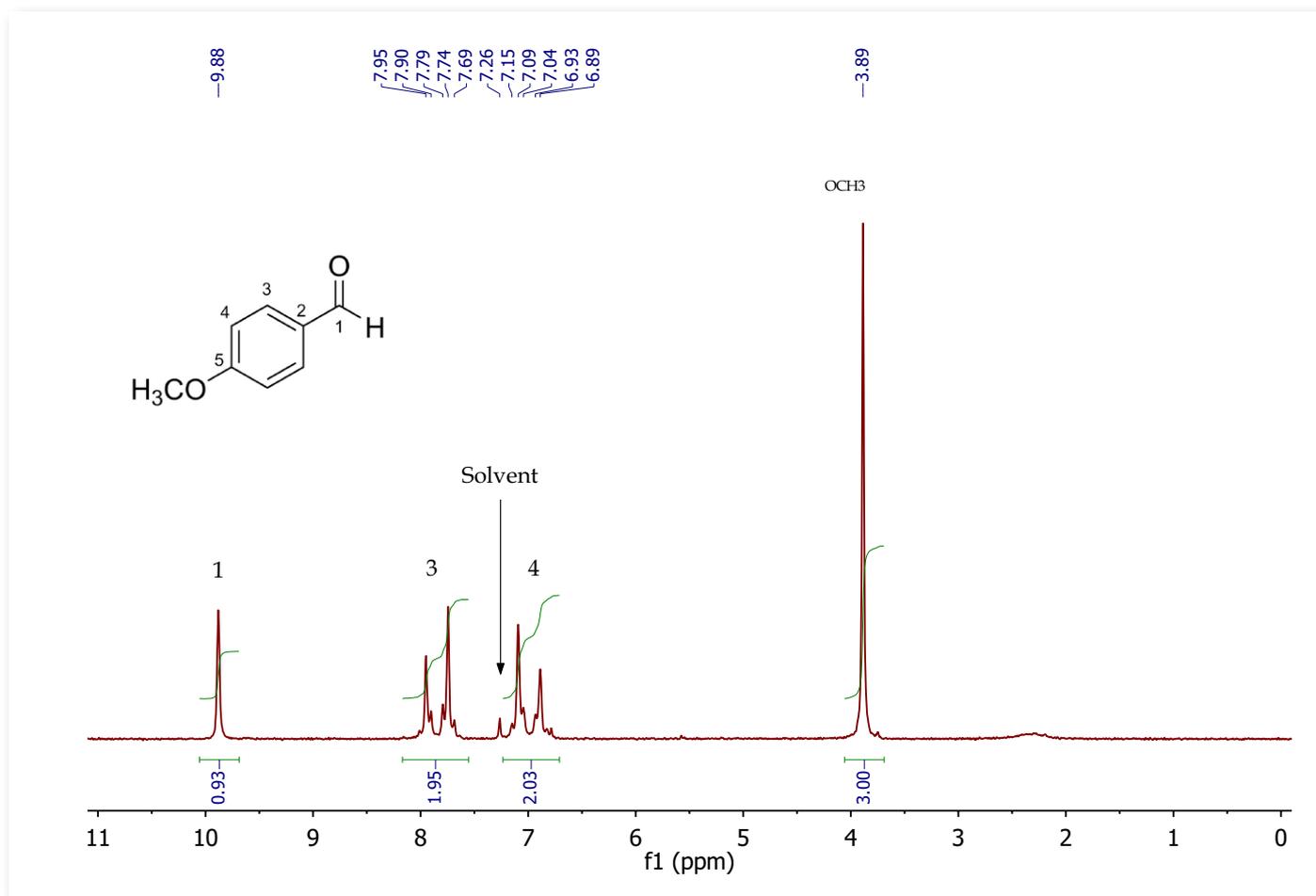


Figure 2. <sup>1</sup>H NMR spectrum of *p*-anisaldehyde in CDCl<sub>3</sub>.

The <sup>1</sup>H NMR spectrum for the starting material, *p*-anisaldehyde, is shown in Figure 2. Here, the resonances for the aldehyde and oxymethyl proton environments can be easily identified. The two remaining resonances, belonging to the 1,4-disubstituted benzene ring, can be assigned based on inductive effects of the substituents, *i.e.* the aldehyde carbonyl group pulls electron density away from the aromatic ring, deshielding the *ortho* protons and shields those in the *meta* position. The oxymethyl group has the opposite effect.

Figure 3 shows the <sup>1</sup>H NMR spectrum of recrystallized 4-(4'-methoxyphenyl)-3-buten-2-one. The diagnostic methyl resonances at 2.35 ppm and 3.83 ppm are the terminal methyl at position 1 and oxymethyl on the aromatic ring, respectively. The remaining resonances between 6.37–7.69 ppm

should account for the remaining six protons in four chemical environments – *i.e.* the two alkene protons and the two sets of aromatic protons. The overlap of these resonances complicates the assignment of their chemical shifts and multiplicities. By turning to the 2D *J*-resolved and COSY experiments in Figures 4 and 5, this region can be observed in more detail.

In the 2D *J*-resolved experiment, *J*-coupling constants are mapped against the proton chemical shift. This allows the chemical shifts of proton resonances to be accurately measured by examining the f2 dimension, while their coupling constants can be measured in the f1 dimension. Thus, in Figure 4, two doublets with 16.4 Hz coupling constants can be identified at 6.56 and 7.51 ppm, and two doublets of 8.5 Hz at 6.89

and 7.50 ppm. The magnitude of the coupling constants obtained here also point to the location of each spin system – 16.4 Hz is typical for a 1,2-disubstituted alkene with an *E* geometry, while 8.5 Hz is consistent with protons on an aromatic ring in an *ortho* arrangement.

The COSY experiment is used to identify spin-coupling partners, usually over 2–4 bonds. In the COSY of Product A (Figure 5), the same proton pairs identified in the 2D *J*-resolved experiment are shown to correlate to each other through interpretation of cross-peaks read from the diagonal of the 2D spectrum. Thus, the resonances at 6.89 ppm and 7.50 ppm (green box) form one spin system, while the resonances at 6.56 ppm and 7.52 ppm (blue box) form the other spin system. These correlations further validate the proximity of these resonances to each other.

Assignment of these proton resonances to their actual positions in the molecule can be made based on the inductive effects of the nearby functional groups.<sup>2</sup> The alkene protons of an  $\alpha,\beta$ -unsaturated carbonyl compound are affected by the electron-withdrawing carbonyl group in different ways; the  $\beta$ -proton is shielded (lower ppm) and the  $\alpha$ -proton is deshielded (higher ppm). Hence, the protons on C-3 and C-4 can be assigned as 6.56 ppm and 7.51 ppm, respectively. The oxymethyl group attached to C-4 of the aromatic ring has a similar effect. The protons situated *ortho* to the ether group are shielded, while the *meta* protons are deshielded. This allows the remaining protons, at positions C-2' and C-3', to be assigned as 7.50 ppm and 6.89 ppm, respectively.

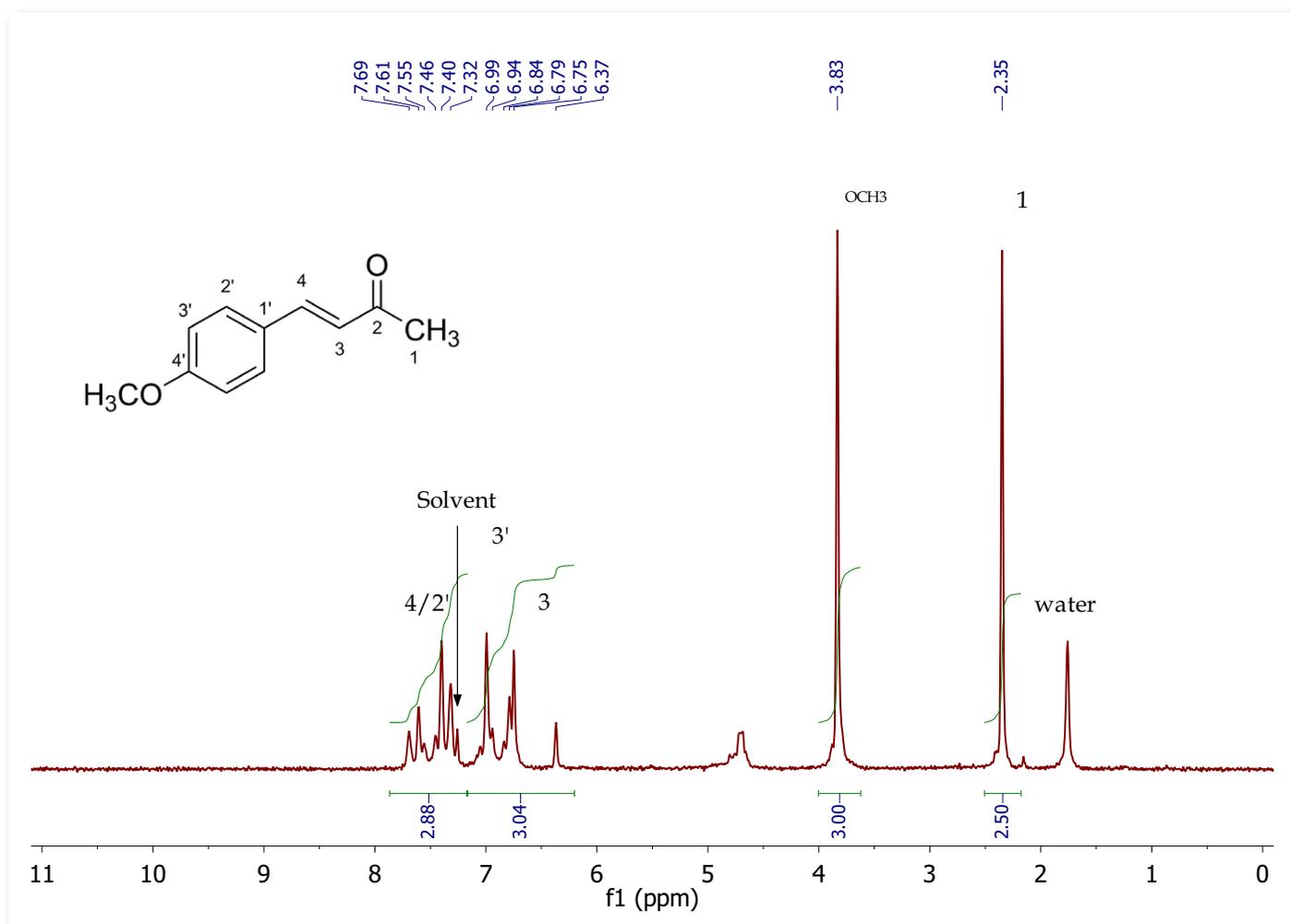


Figure 3. <sup>1</sup>H NMR spectrum of 4-(4'-methoxyphenyl)-3-buten-2-one (Product A) in CDCl<sub>3</sub>.

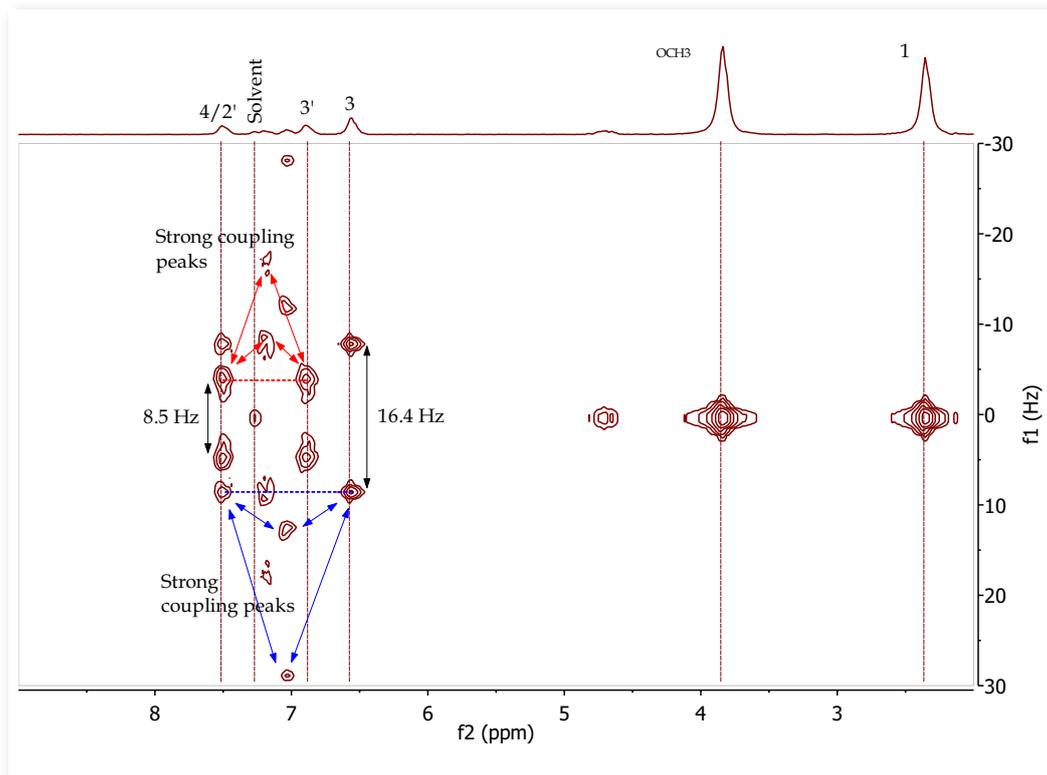


Figure 4. 2D J-resolved spectrum of 4-(4'-methoxyphenyl)-3-buten-2-one (Product A) in CDCl<sub>3</sub>.

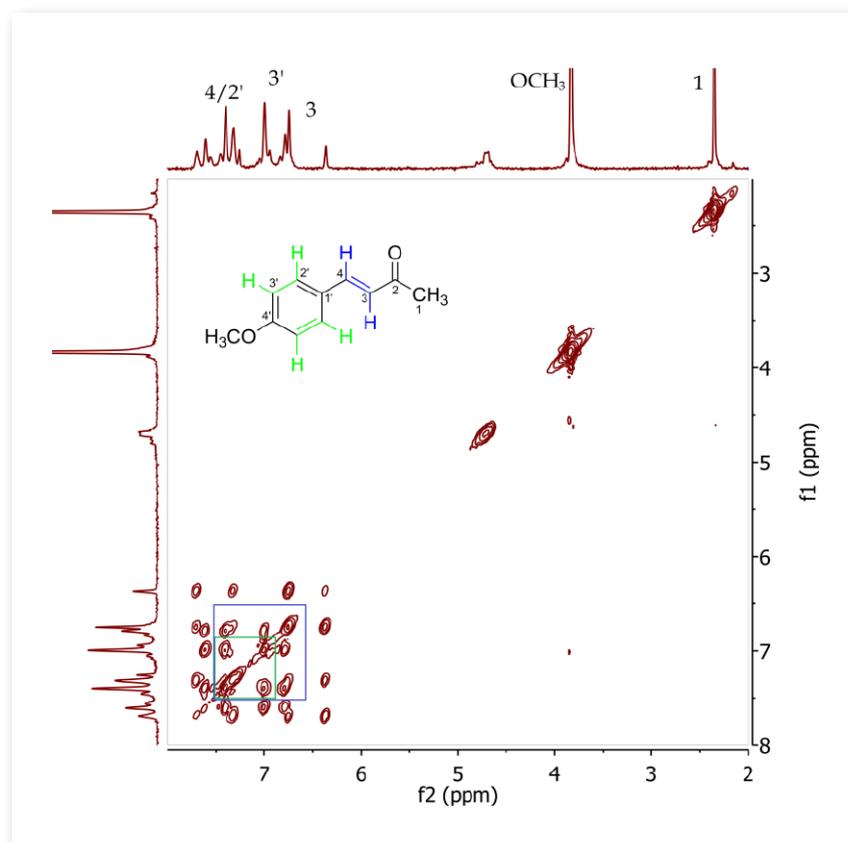


Figure 5. COSY spectrum of 4-(4'-methoxyphenyl)-3-buten-2-one (Product A) in CDCl<sub>3</sub>.

## Preparation of 1,5-bis(4'-methoxyphenyl)-1,4-pentadien-3-one (Product B)

In a 100 mL round bottom flask, prepare a solution of freshly recrystallized 4-(4'-methoxyphenyl)-3-buten-2-one (0.60 g, 3.4 mmol) and *p*-anisaldehyde (0.61 mL, 5.1 mmol) in ethanol (15 mL). In a separate beaker, prepare a solution of potassium hydroxide (0.8 g) in water (20 mL) and add slowly

(over 2 minutes) to the mixture in the round bottom flask while stirring. Stir the solution for 30 minutes. Recover the resulting solid by vacuum filtration and wash with water. Dry the solid and recrystallize from ethanol (Figure 6).



Figure 6. Recrystallized 1,5-bis(4'-methoxyphenyl)penta-1,4-dien-3-one (Product B).

## NMR Spectra

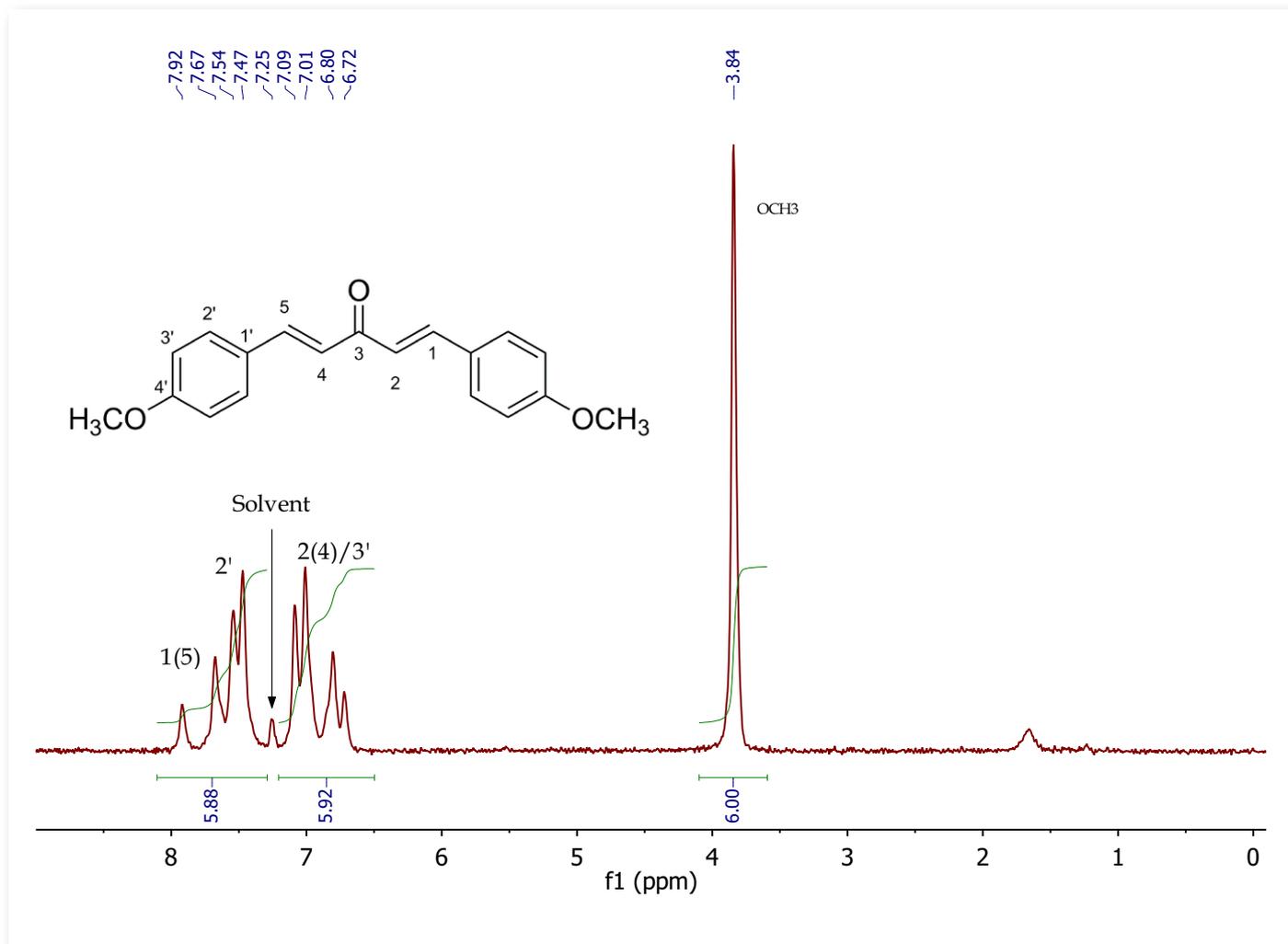


Figure 7. <sup>1</sup>H NMR spectrum of 1,5-bis(4'-methoxyphenyl)-1,4-pentadien-3-one (Product B) in CDCl<sub>3</sub>.

The <sup>1</sup>H NMR spectrum of 1,5-bis(4'-methoxyphenyl)penta-1,4-dien-3-one (Figure 7) confirms the loss of the reactive methyl centre of Product A upon reaction with *p*-anisaldehyde. Again, interpretation of the downfield resonances between 6.82–8.02 ppm requires use of the 2D *J*-resolved and COSY experiments (Figures 8 and 9, respectively).

From the *J*-resolved experiment, two doublets, centred at 6.90 ppm, with coupling constants of 8.6 and 16.4 Hz, can be discerned. Further downfield, a 8.9 Hz doublet at 7.57 ppm and a 16.0 Hz doublet at 7.73 ppm can be identified. With this information, the two spin systems in the COSY spectrum (Figure 9) can be identified much

easier – one spin system between 6.90 ppm and 7.57 ppm (green box) and the other between 6.90 ppm and 7.73 ppm (blue box). Using the same argument as above for assigning relative positions, the alkene protons on C-1/C-5 and C-2/C-4 can be assigned as 7.73 ppm and 6.90 ppm, respectively. Likewise, the aromatic protons on C-2' and C-3' are 7.57 ppm and 6.90 ppm, respectively. The *E*-geometry of the alkene is again confirmed from the magnitude of the coupling constants of H-1/H-5 and H-2/H-4.

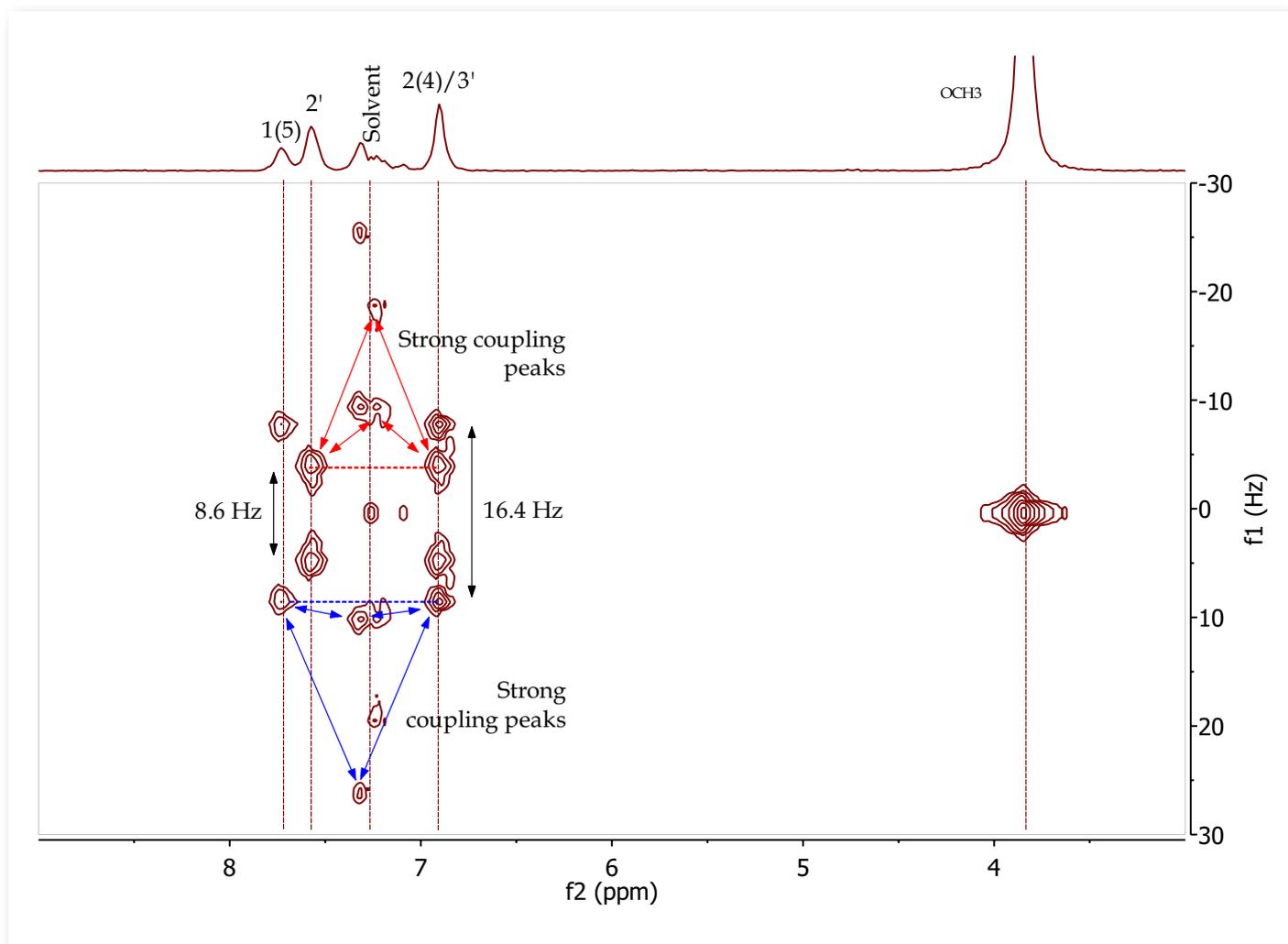


Figure 8. 2D  $J$ -resolved spectrum of 1,5-bis(4'-methoxyphenyl)-1,4-pentadien-3-one (Product B) in  $\text{CDCl}_3$ .

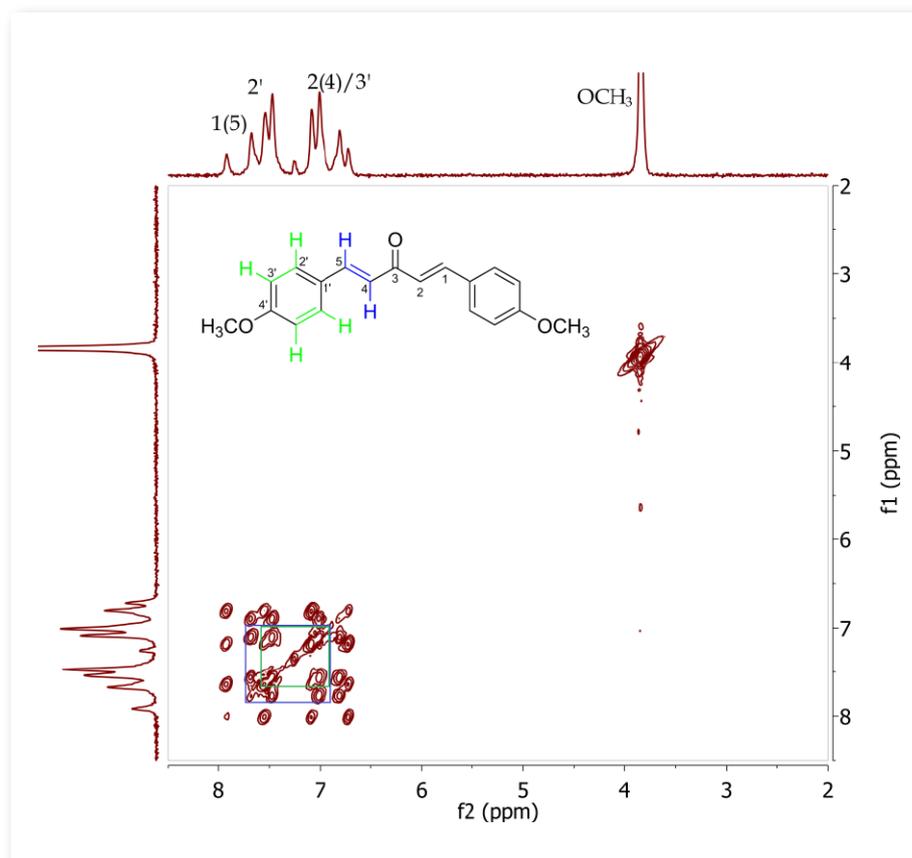


Figure 9. COSY spectrum of 1,5-bis(4'-methoxyphenyl)-1,4-pentadien-3-one (Product B) in  $\text{CDCl}_3$ .

### Tasks & Questions

- For each reaction, record the mass of recrystallized product and calculate the yield.
- Obtain  $^1\text{H}$ , COSY and 2D JRes NMR spectra of the recrystallized products (approximately 50 mg) in  $\text{CDCl}_3$  (1 mL) using the Spinsolve spectrometer.
- What is the rationale behind the alkene geometry observed for each product?

### Conclusion

This experiment has demonstrated an important reaction in synthetic organic chemistry. With the use of 1D- and 2D-NMR experiments, key aspects of the chemistry, structure and geometry for these compounds – both in synthetic preparation and characterization – can be rationalized.



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## References

- 1) Jones, Jr., M. Organic Chemistry, 2nd ed., W. W. Norton & Company, Inc., 2000.
- 2) Silverstein, R. M.; Webster, F. X. Spectrometric Identification of Organic Compounds, 6th ed., John Wiley & Sons, 1998.

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