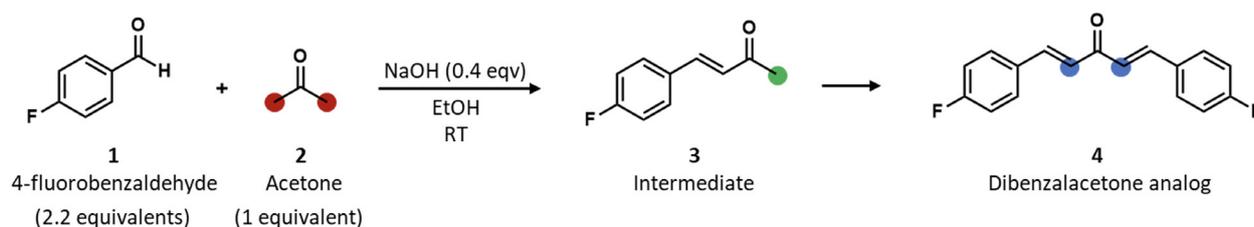


Monitoring a Claisen-Schmidt Condensation Reaction by NMR in the teaching Class



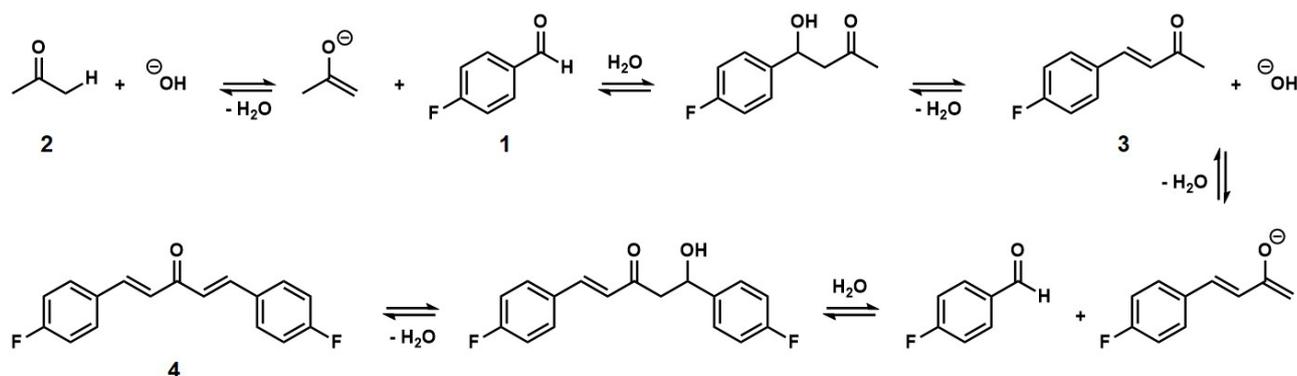
Scheme 1. Claisen-Schmidt condensation reaction for the synthesis of dibenzalacetone analog

The development of high-performance benchtop NMR spectrometers provides a practical and information-rich way to monitor on-line/in-line the progress of chemical reaction. NMR provides not only the structural information about the different chemical species involved in the reaction but also quantitative information about the concentration of reactants and products. By following the conversion in real time, chemists get the required insight to understand the kinetics of the reaction. Another advantage of using NMR for reaction monitoring is the ability to observe reaction intermediates. These can often be missed with endpoint reaction analysis, since intermediate, by definition, gets produced in the early stage and consumed during later stage of the reaction.

In recent years, the availability and affordability of benchtop NMR systems have offered the opportunity for schools to incorporate NMR spectroscopic techniques into organic chemistry curricula. With simple button-clicking, instructors and students can perform different NMR experiments to confirm the reaction products, or to monitor a reaction with NMR. This application note describes an example of using the Spinsolve 60 MHz Carbon ULTRA to monitor a frequently used reaction in the organic chemistry laboratory – the Claisen-Schmidt (or cross-aldol, Scheme 1) condensation reaction to synthesize dibenzalacetone. Students can visualize the kinetic profile of different chemical components in real-time. They can also observe the reaction intermediate, which is a concept that is seldomly demonstrated in laboratory experiment since intermediate species are not easily isolated from the reaction mixture for characterization. With the hands-on experience in the lab, students will develop a deeper understanding of chemistry concepts that they learn in lectures and familiarize themselves with the modern NMR techniques being adopted in industry.

Background and practical significance

Dibenzalacetone (or dibenzylideneacetone, abbreviated as DBA) and its analogs are organic compounds with high degree of conjugated π bond system with many important applications such as being active ingredients in sunscreens, or ligands in coordination chemistry [1]. DBA and its analogs can be synthesized from a classic Claisen-Schmidt (cross-aldol) condensation between acetone and benzaldehyde derivatives, with the reaction mechanism shown in Scheme 2. Under basic condition, hydroxide ion deprotonates acetone 2 at its α -position to form an enolate. This nucleophilic enolate reacts with 4-fluorobenzaldehyde 1 to form a β -hydroxy ketone, which readily undergoes dehydration to produce intermediate 3. Since acetone can be deprotonated at both its α -position to form reactive enolate species, one acetone molecule can react consecutively with two benzaldehyde molecules to form the symmetrical DBA product. This reaction has been adapted in many undergraduate organic chemistry laboratory curricula, due to the simple reaction set-up and the discussion of an important organic reaction – the aldol condensation mechanism.



Scheme 2. Mechanism of Claisen-Schmidt reaction

Reaction set-up and conditions

For the reaction described in this application note and depicted in Scheme 1, 4-fluorobenzaldehyde (1) and acetone (2) were chosen as starting material to generate 4-(4-fluorophenyl)-3-buten-2-one (3) as an intermediate as well as the major product known as DBA analog [1,5-bis(4-fluorophenyl)-1,4-pentadien-3-one, (4)]. Compound 1 was used in excess (2.2 equivalents) to ensure the completion of the reaction.

This experiment was designed to focus on observing the reaction progress in real-time using the Spinsolve NMR spectrometer. The reaction was carried out in a 5-mm NMR tube. 4-fluorobenzaldehyde (1) solution in absolute ethanol (0.25 mL of 1.32 M solution, 0.33 mmol) and acetone (2) solution in absolute ethanol (0.25 mL of 0.6 M solution, 0.15 mmol) were added to the NMR tube. The content was mixed for 20 seconds. Then, sodium hydroxide solution in absolute ethanol (0.1 mL of 0.6 M solution, 0.06 mmol) was added. The content was mixed for 20 seconds. The NMR tube was inserted into a Spinsolve 60 MHz Carbon Ultra for data acquisition. Since the solvent of the reaction was protonated ethanol, a 1D PRESAT solvent suppression sequence with ^{13}C decouple capabilities was used to monitor the reaction progress. The Spinsolve spectrometers are equipped with a built-in external lock system, therefore the NMR analysis of samples in protonated solvents (without deuterated solvents) are possible.

Results of reaction monitoring study

Before setting up the reaction for the real-time monitoring experiment, the spectra of the reactants in ethanol were analyzed separately to determine the optimal parameters for data acquisition, and to identify the regions of interest in the spectra to quantify the different chemical species of the reaction. Figure 1 shows a stack plot with the 1D proton spectra of the two reactants (blue and green) and the reaction mixture before NaOH solution was added (red). These spectra were acquired with the solvent suppression protocol to reduce the magnitude and tails of the three ethanol signals. The ^1H NMR spectrum of 4-fluorobenzaldehyde 1 (blue spectrum) shows the aldehyde proton at 9.1 ppm. Since this signal is well separated from the rest of the signals in the ^1H NMR spectrum of the reaction mixture (red spectrum), it will be integrated to monitor the amount of 1 in the reaction mixture. The ^1H NMR spectrum of acetone 2 in ethanol shows the singlet corresponding to the methyl groups at 1.5 ppm. Since protonated ethanol was used as a solvent, ^{13}C satellites of the main triplet (CH₃ group) and quartet (CH₂ group) can be observed in the ^1H NMR spectra of aldehyde 1 and acetone 2. In the case of acetone, one of the ^{13}C satellite signals overlaps with the methyl singlet of 2, interfering with the integration value of its signal. Therefore, the ^{13}C decoupling option was employed during the acquisition of ^1H NMR spectrum of the reaction mixture (red spectrum). In this spectrum, the ^{13}C satellites have been removed and the singlet at 1.5 ppm has a clean baseline with no overlapping to allow for an accurate quantification of 2. The NMR spectra shown in Figure 1 were acquired with only 2 scans (40 seconds) allowing the concentration of reaction components to be measured accurately with high signal-to-noise ratio.

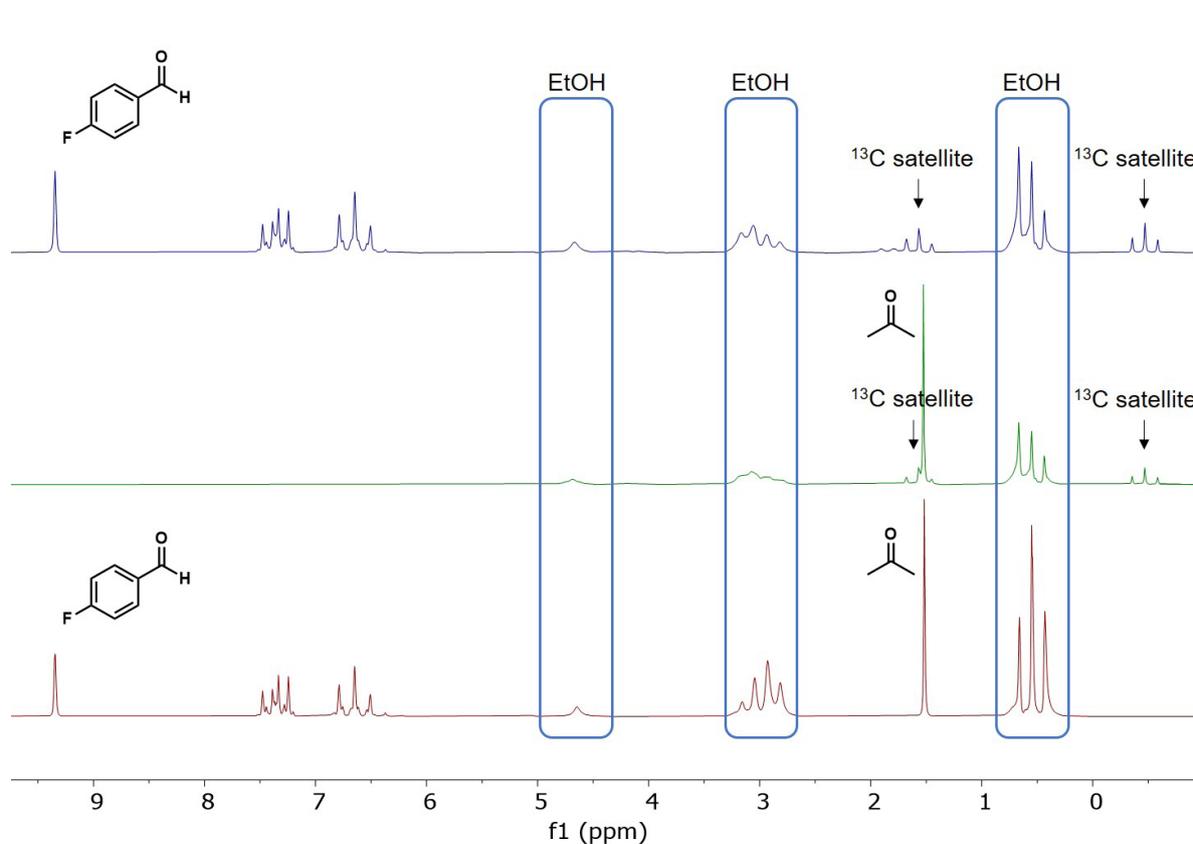


Figure 1. ^1H NMR spectra of 4-fluorobenzaldehyde 1 in ethanol (blue), acetone 2 in ethanol (green), and both reactants in ethanol with ^{13}C decouple protocol (red)

The reaction was monitored for about 80 minutes with a total of 60 1D proton spectra acquired. These spectra are displayed in the stack plot (Figure 2), with the increasing reaction time going up the vertical axis. Four integral regions were defined to monitor different chemical components. Their integral values are plotted over time in Figure 2. The integral value of 2 (red integral region) decreased rapidly during the first 20 minutes of the reaction. The rate of conversion of 2 then slowed down, until 2 was completely consumed towards the end of the experiment.

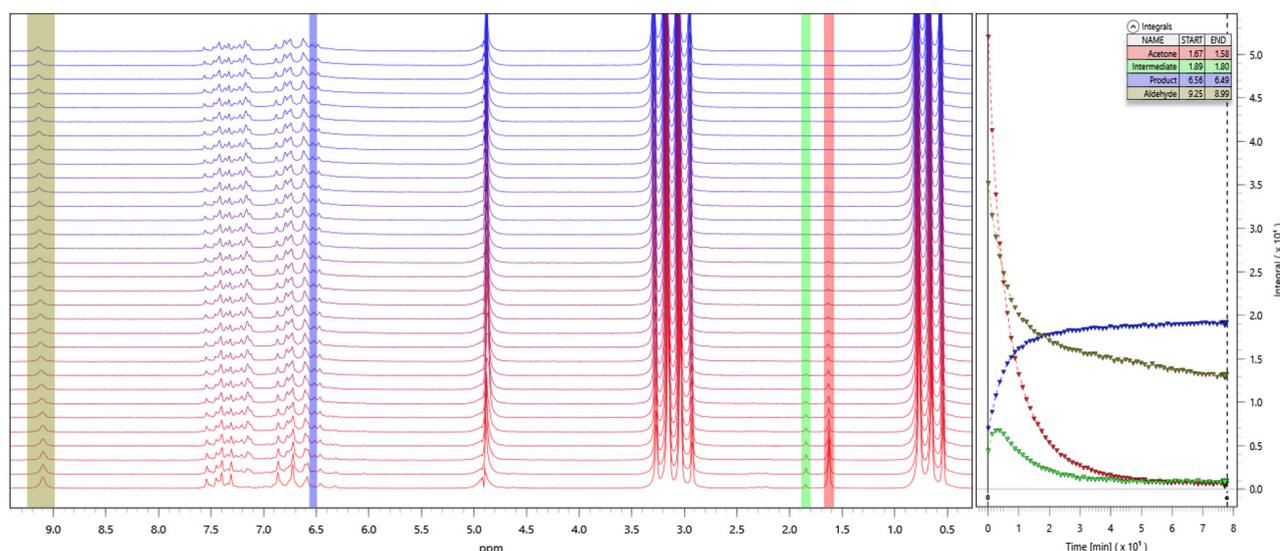


Figure 2. Left: Stack plot of ¹H NMR spectra of the reaction progress; Right: integral over time plot of the defined integral regions.

The diagnostic signal of aldehyde 1 can be observed as a singlet at 9.1 ppm (brown integral region). The plot of this integral shows at the beginning a similar pattern as the one of acetone 2. It decreased rapidly during the first 20 minutes, but then the consumption rate slowed down and remained almost constant for the rest of the reaction. Since aldehyde 1 was added to the reaction in excess, its signal was still observed at the end of the experiment.

During the progress of the Claisen-Schmidt reaction, a singlet was observed at 1.85 ppm (green integral region). The chemical shift and multiplicity of this signal match the expected signal of the methyl group in intermediate 3. The plot for this singlet showed characteristic of an intermediate species, where its concentration increased during the first five minutes of the reaction, then slowly decreased until it was undetectable in the reaction mixture. Therefore, this signal was assigned to the methyl group in the intermediate 3 (Scheme 1 and 2) where the acetone 2 had reacted with only one molecule of 4-fluorobenzaldehyde 1. The presence of intermediate 3 in the reaction mixture can provide an explanation for the slower consumption rate of acetone 2 after 20 minutes. Since intermediate 3 undergoes a similar chemical transformation as acetone 2 (Scheme 2), it can compete with acetone, therefore decreases acetone's consumption rate towards the end of the experiment.

The blue integral region covered a new signal that appeared in the complex aromatic region due to the coupling between proton and fluorine on the benzene rings in both reactants and product. This signal was assigned to the allylic protons on the α -carbon of the ketone group in the final product 4. The concentration of the final product (blue curve in Figure 2) increased at a high rate at the beginning of the reaction, then slowed down to almost reach a plateau towards the end of the experiment.

Conclusion

Using the Spinsolve Benchtop NMR spectrometer to monitor the progress of this cross-aldol reaction helps demonstrate important concepts in organic chemistry. The real-time plot of ^1H NMR integral value over time allows students to observe how the concentration of reactants and products changes as the reaction progresses. The presence of acetone 2 in the reaction mixture was easily observed through NMR. This could not have been done with the common method for monitoring reaction such as thin layer chromatography (TLC) due to high volatility of acetone. Furthermore, the structural information and kinetic profile obtained from the Spinsolve real-time data visualization helps identify the reaction intermediate 3. With a simple set up of the Spinsolve benchtop NMR spectrometer and standard NMR tubes, the reaction can be performed in a laboratory period to provide students an enhanced learning experience, further solidify the concepts that students learn in lecture.

Reference

[1]. Meszaros, M., Russo, T. Journal of Chemical Education, **1999**, 76, 69-70

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