

Thermo Scientific picoSpin 45 Nuclear Magnetic Resonance Aldol Condensation Reaction

Dean Antic, Ph.D., Thermo Fisher Scientific, Boulder, CO, USA

Key Words

picoSpin 45 Nuclear Magnetic Resonance (NMR) Spectrometer, Aldol Condensation, Chemical Education, Splitting Patterns, Substituent Effects, Teaching

A solid understanding of NMR spectroscopy is a basic learning goal for any student of chemistry. The hands-on approach to learning is the most powerful method for instructors in both classroom settings and in the teaching laboratory. Direct experience with acquiring and processing NMR spectra to determine product purity or to monitor the course of a chemical reaction is extremely valuable, especially for organic chemistry students.

The challenges for teaching lab directors and instructors of organic chemistry in applying modern NMR techniques are manifold:

- Accessing modern high-field research NMR facilities for student instruction
- Managing complex and technically challenging instrumental operations
- Funding expensive equipment dedicated solely to teaching
- Housing oversized instrumentation in existing lab space
- Developing NMR applications to complement existing lab curricula
- Allowing students direct access to an expensive instruments
- Gaining or maintaining American Chemical Society (ACS) or other national accreditation by incorporating NMR into the curriculum



The Thermo Scientific™ picoSpin™ 45 NMR spectrometer is your key to solving all of these problems. In this application note, we illustrate the use of the picoSpin 45 in teaching through the aldol condensation reaction.

In many undergraduate organic teaching programs, the aldol condensation reaction is the first exposure students have to NMR as an analytical tool.¹⁻⁵ While the technical aspects of executing the aldol reaction are not difficult, the analysis of products is challenging since this is frequently a student's first time using NMR instrumentation, interpreting NMR spectra and evaluating the outcome of their synthetic efforts. Because of the simplicity of its design and ease of use, the aldol condensation lab is a good entry point for applying the picoSpin 45 spectrometer in a teaching laboratory.

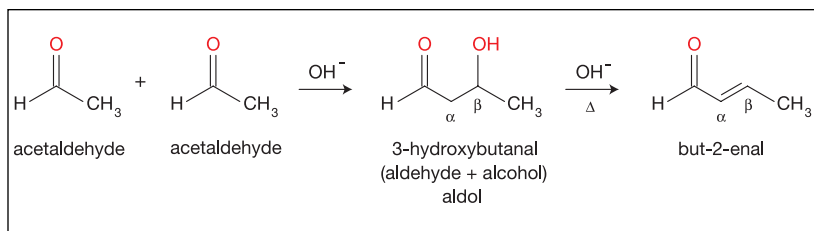


Figure 1: Aldol self-condensation of acetaldehyde

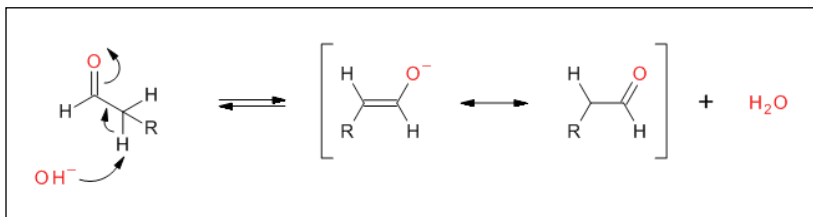


Figure 2: Base-catalyzed production of the enolate ion in the aldol self-condensation reaction (R = H, alkyl, phenyl)

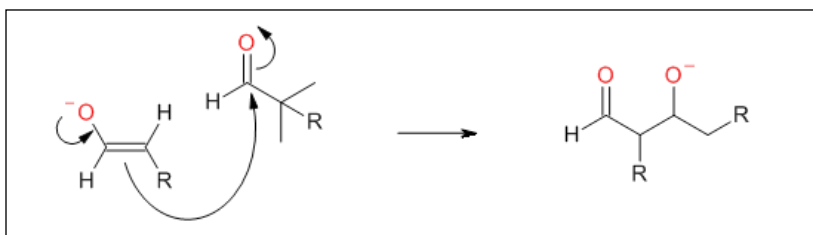


Figure 3: Nucleophilic addition of enolate anion to the carbonyl group (R = H, alkyl, phenyl)

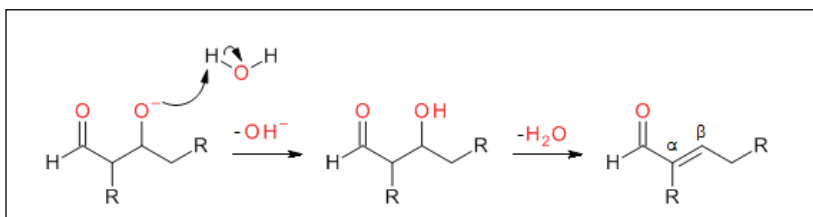


Figure 4: Formation of the aldol product and dehydration to an α,β -unsaturated carbonyl product

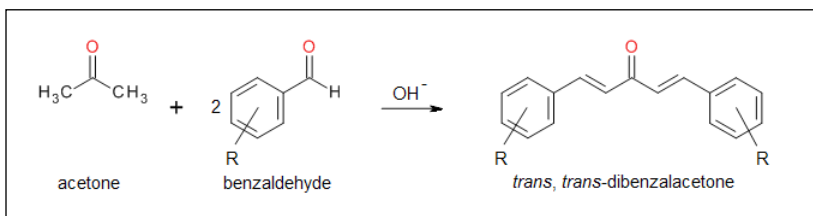


Figure 5: Crossed aldol condensation reaction, producing the α,β -unsaturated ketone dibenzalacetone

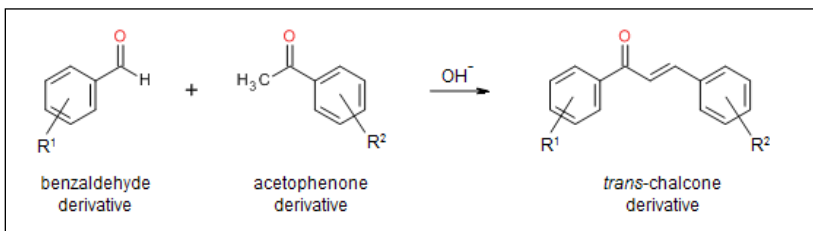


Figure 6: Crossed aldol condensation reaction, producing the α,β -unsaturated ketone chalcone

Aldol condensation reactions represent an important class of reactions for forming carbon-carbon bonds. In the aldol reaction, two carbonyl compounds are condensed to form a β -hydroxyaldehyde or β -hydroxyketone – the aldol product. The classic aldol reaction is a “self-condensation” of the reactant aldehyde or ketone where one molecule adds to another of the same type. An example of a self-condensation aldol reaction is shown in Figure 1, using acetaldehyde as the sole reactant.

Here, the aldol product, 3-hydroxybutanal, is the result of adding acetaldehyde to another acetaldehyde reactant molecule to form the **aldol** (aldehyde-alcohol) product.

When carried out under base-catalyzed conditions, the aldol reaction proceeds via an enolate ion (Figure 2). The resonance stabilized enolate then undergoes nucleophilic addition to the carbonyl carbon of another aldehyde or ketone molecule, forming a new C-C bond and an alkoxide ion (Figure 3).

The β -hydroxy aldehyde or ketone is then formed in the next step by reaction with water, and the reaction is finalized by dehydration of the alcohol group in a strong base, resulting in the loss of water and the formation of an α,β -unsaturated product (Figure 4).

Similar self-condensation reactions will occur for ketones, as well as derivatized aldehydes and ketones, so long as an enolizable proton at the α carbon position exists.

Crossed aldol reactions between aldehydes and ketones result in the formation of mixed condensation products. Here, the enolate ion of one compound undergoes nucleophilic addition to the carbonyl carbon of a different compound. Crossed-condensation products are usually undesirable since they result in a mixture of products, and reduce the yield of a desired product.

Careful selection of starting materials where only one reactant has an enolizable α hydrogen can minimize the formation of mixtures. This is illustrated in Figures 5 and 6 where an aromatic aldehyde, benzaldehyde, is substituted for the alkylaldehyde as a reactant.

Derivatives of the parent reactant molecules benzaldehyde and acetophenone can include a variety of R, R¹ and R² functional groups, such as methyl (-CH₃), methoxy (-OCH₃), chloro (-Cl), bromo (-Br), amino (-NH₂), hydroxy (-OH), nitrile (-CN), etc. and in various positions around the phenyl ring. Due to intermolecular hydrogen bonding, the hydroxy group will show temperature, concentration and solvent polarity dependence, which complicates interpretation. Similarly, complications will arise in the spectrum of the amino group due to spin coupling of the proton with the nitrogen nucleus, the variable rate of exchange of the labile amino proton and the electric quadrupole moment of the ¹⁴N nucleus. Halogen substitution does not introduce a new peak in a proton NMR spectrum but will affect peak positions and splitting patterns on the aromatic protons. Only the methyl and methoxy groups introduce new, non-overlapping resonance lines in the parent molecule spectrum, which affords straightforward interpretation.

¹H NMR – A Qualitative Lesson

It is easy to identify the prominent peaks in the ¹H NMR spectra of the reactants in the aldol reactions of Figures 5 and 6. Both the aldehyde proton and methyl-ketone protons produce only one resonance line each, thus making them simple to monitor. NMR spectra can be measured on pure samples or using an aliquot of the reaction mixture.

The picoSpin 45 NMR spectrometer is ideal for preliminary qualitative analysis of neat samples and mixtures, giving students the opportunity to determine the quality of their starting materials, establish the stoichiometry of their mixture, identify the predominant functional groups which undergo chemical transformation, and gain valuable hands-on experience using NMR in the lab. Because the capillary cartridge can be quickly flushed and refilled, it can be used during a 3–4 hour organic chemistry lab experiment. Students can sample their reaction mixture multiple times at various stages throughout their experiment, obtaining spectra as the reaction proceeds and measuring a spectrum of isolated product. ¹H NMR spectra shown here were acquired with a 90-degree pulse angle, 750 ms acquisition time, 10–20 s recovery delay, and are an average of 9 or 49 scans.

Spectra of reactants 4-methoxybenzaldehyde and 4-methylbenzaldehyde are shown in Figures 7 and 8. The aldehydic proton produces a lone signal due to a lack of neighboring proton. Diamagnetic anisotropy arises from circulating π electrons of the carbonyl (C=O) bond induced along the transverse axis by the applied field, giving rise to strong deshielding of this lone proton. In the spectrum of 4-methoxybenzaldehyde, the aldehyde proton appears as a singlet at 9.90 ppm, while for 4-methylbenzaldehyde this same signal is at 10.08 ppm.

Protons of the methoxy methyl group experience deshielding due to carbon bonding to an electronegative oxygen atom and shift downfield, producing a singlet at 3.79 ppm. There are four aromatic protons that are in two different chemical environments, generating a characteristic doublet of doublets splitting pattern. Protons ortho (position 2 and 6) to the aldehyde are in the deshielding zone of the carbonyl bond, whereas protons in the meta position (3 and 5) move upfield due to resonance shielding by the adjacent methyl ester.

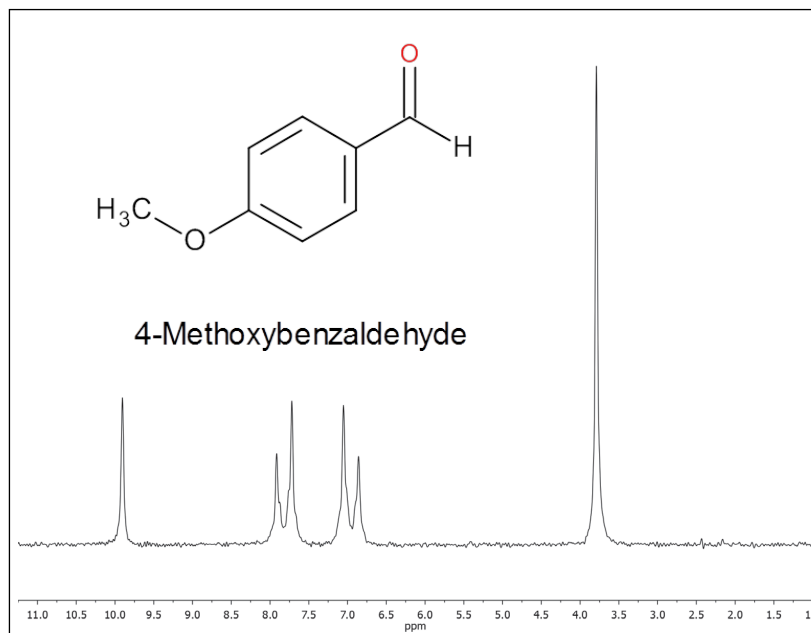


Figure 7: NMR spectrum of 4-methoxybenzaldehyde (neat, 25 scans)

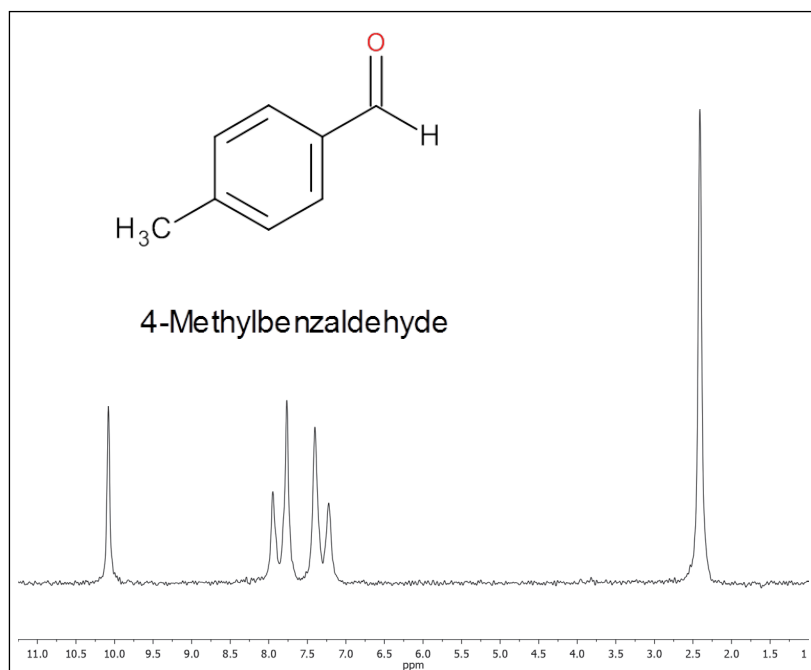


Figure 8: NMR spectrum of 4-methylbenzaldehyde (neat, 25 scans)

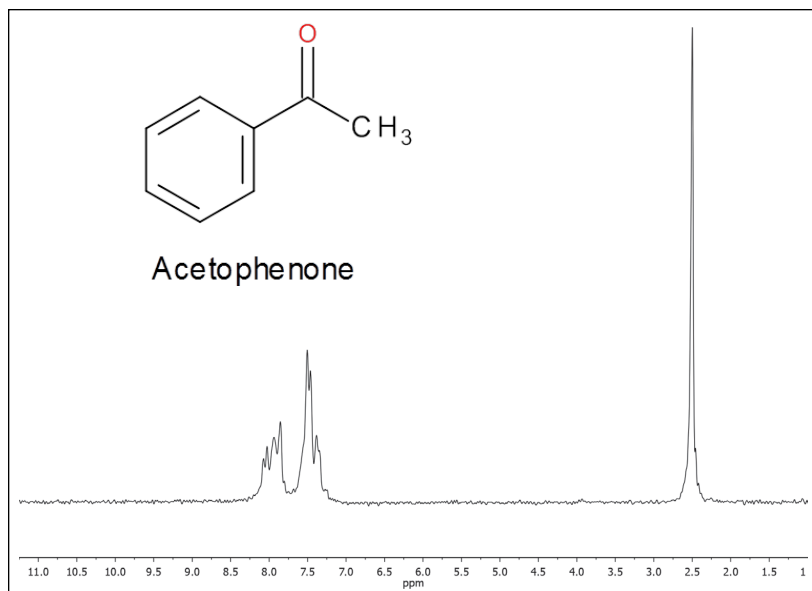


Figure 9: NMR spectrum of acetophenone (neat, 25 scans)

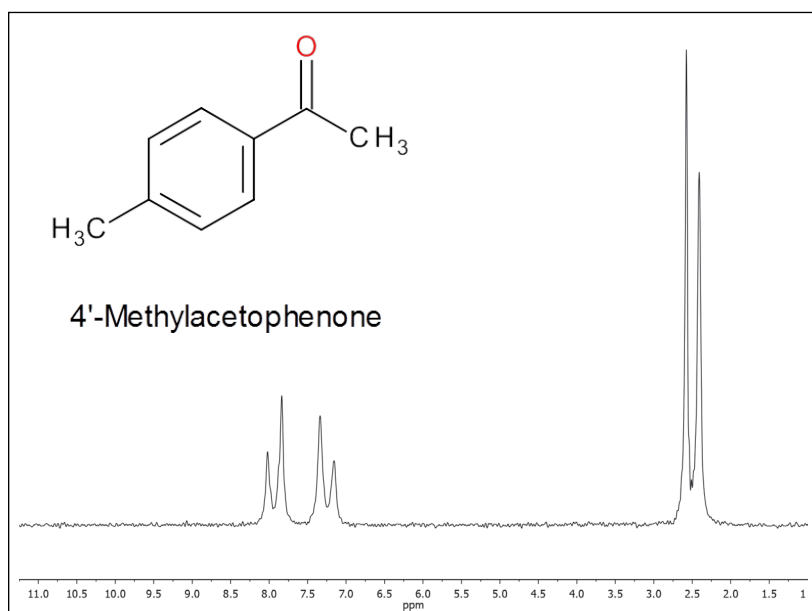


Figure 10: NMR spectrum of 4'-methylacetophenone (neat, 25 scans)

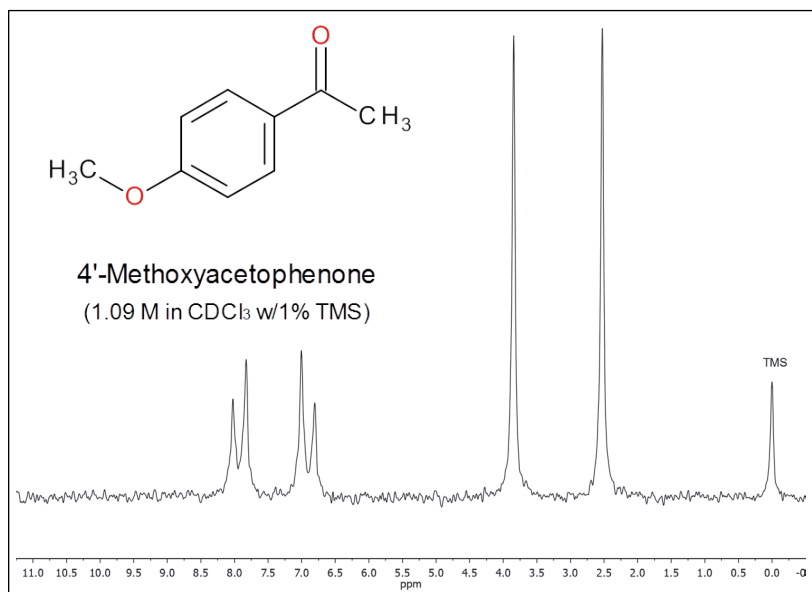


Figure 11: NMR spectrum of a 4'-methoxyacetophenone in CDCl_3 (1.08 M, 64 scans)

Ring currents in the aromatic group produce similar anisotropy, deshielding the in-plane protons of the benzene ring. Lower symmetry arising from asymmetric para disubstitution of the benzene ring affects the chemical environment for protons in the ortho (2 and 6) and meta (3 and 5) positions, giving rise to a doublet of doublets signal. Ortho protons further deshielded by the adjacent aldehyde group appear downfield ($\delta 7.81$), while the meta protons appear upfield ($\delta 6.95$) with respect to a center frequency of $\delta 7.38$ – each proton being split by one nearest neighbor proton, giving rise to a doublet of doublets signal. Integration of peak areas reveals an expected 1:4:3 proton ratio for both 4-methoxybenzaldehyde and 4-methylbenzaldehyde.

Like the substituted benzaldehydes in Figures 7 and 8, the proton NMR spectrum of acetophenone (Figure 9) exhibits multiple peaks in the 7.3–8.2 ppm region, but the splitting pattern is complicated by overlap of signals from five phenyl protons in three different chemical environments. At first glance, the signal pattern in the aromatic region appears as a doublet of triplets signal, but closer scrutiny of the splitting pattern and asymmetric signal intensity reveals overlapping multiplicities. Protons in positions 2 and 6 (ortho) are each split by neighboring protons in positions 3 and 5 (meta), producing doublet signals. The para proton is split by two adjacent and identical protons (3 and 5) into a triplet signal which overlaps strongly with the doublet signal from the meta protons. Ortho protons shift farther downfield due to deshielding by the aldehyde group, and their signal is easily resolved.

The three keto-methyl protons experience less shielding and shift to ~ 2.6 ppm, producing only a single peak. Peak area integration shows a 3:5 ratio. By comparison, the reactant acetone would produce a similar signal and chemical shift ($\delta 2.5$) but with an integral area equivalent to six homotopic protons for the absorption peak.

Substitution by a methyl group in the para position in 4'-methylacetophenone (Figure 10) clears up issues with overlapping signals in the aromatic region, showing only ortho and meta protons being split by each other. The addition of a methyl group on the benzene ring introduces an alkyl signal ($\delta 2.34$) near the keto-methyl one ($\delta 2.50$), but this is clearly resolved in the spectrum.

Replacing the methyl substituent in the para position of 4'-methylacetophenone with a methoxy group in 4'-methoxyacetophenone (Figure 11) separates the two methyl groups by shifting the methoxy methyl downfield to 3.79 ppm. The solid sample 4'-methoxyacetophenone was dissolved in CDCl_3 and its spectrum measured at a concentration of 1.09 M. Considering the concentration of the 4'-methoxyacetophenone solution and sample volume within the spectrometer's RF coil, we are measuring signal arising from approximately 38 nano-moles of material.

The crossed aldol reaction product *trans*-chalcone, derived from the combination of benzaldehyde with acetophenone is shown in Figure 12. This solid sample was dissolved at a concentration of 0.99 M in acetone- d_6 containing 1% TMS. The spectrum consists of two overlapping signal groups; one set arises from phenyl protons and a second set from vinyl protons. The olefinic protons, H_α and H_β , are positioned α and β to the carbonyl of this α,β -unsaturated ketone and appear at 7.50 ppm and 7.80 ppm. It is known that under normal solvent conditions the mesomeric effect produces inductive deshielding at the α -carbon position due to the electron-withdrawing effect of the carbonyl, and assignment of the low field signal at δ 7.80 to H_α is plausible.⁶ However, complexation of the α,β -unsaturated ketone in solvents such as DMSO- d_6 gives rise to steric encumbrance, holding rigid the molecular confirmation and making H_α more accessible to the phenyl ring. A similar effect may exist in acetone as well. This solvent effect causes an anomalous chemical shift whereby the H_α and H_β protons exchange positions, placing the β proton downfield with respect to the α proton signal. Hence, unambiguous assignment of the two signals to either the H_α or H_β protons is not possible without further analysis. Evidence of H-H coupling across the olefinic bond is difficult to discern due to heavy overlap with the phenyl proton signals.

Protons on the phenyl ring adjacent to the carbonyl group are expected to shift downfield relative to phenyl ring protons on the vinyl side. The low frequency doublet-of-doublets signal centered at 8.21 ppm thus belongs to the keto phenyl protons, while the high frequency signals centered around 7.54 ppm can be attributed to the vinyl side phenyl protons. Symmetric and asymmetric substitution at both the 4 and 4' positions can simplify the aromatic region.

This simple analysis is an excellent opportunity for students to learn about substituent effects, splitting patterns, sample preparation and dilution.

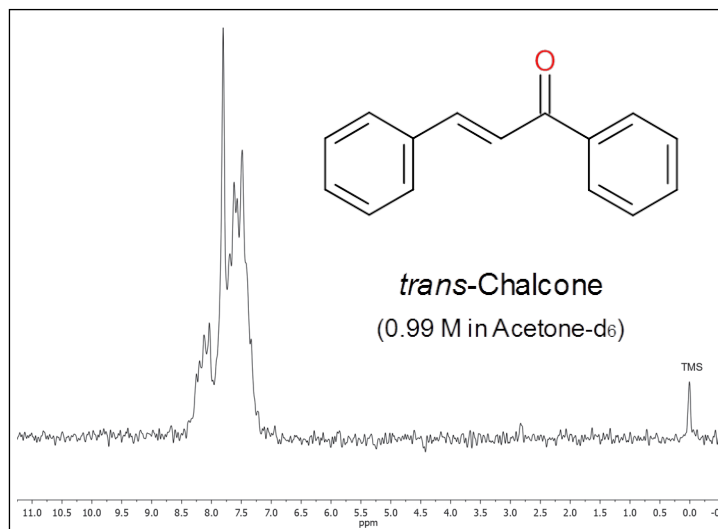


Figure 12: NMR spectrum of *trans*-chalcone (0.99 M, 64 scans)

References

- University of Colorado at Boulder Organic Chemistry Undergraduate Laboratory (<http://orgchem.colorado.edu/>).
- Palleros, D. R., "Solvent-Free Synthesis," *J. Chem. Ed.*, 2004, 81, 1345-1347.
- Hull, L. A., "The Dibenzalacetone Reaction Revisited," *J. Chem. Ed.*, 2001, 78, 226-227. Wade Lab (dibenzalacetone)
- http://en.wikipedia.org/wiki/Aldol_reaction
- SDBSWeb: <http://riodb01.ibase.aist.go.jp/sdbs/> (National Institute of Advanced Industrial Science and Technology, Sept. 30, 2010)
- J-C. Lien, S-C. Chen, L-J. Huang and S-C. Kuo, Solvent Effect of Dimethyl Sulfoxide on the Chemical Shifts of Phenyl Vinyl Ketones, *J. Chinese Chem. Soc.*, 2004, 51, 847-852. (http://proj3.sinica.edu.tw/~chem/servxx6/files/paper_8037_1269164467.pdf)

www.thermoscientific.com

©2013 Thermo Fisher Scientific Inc. All rights reserved. All trademarks are the property of Thermo Fisher Scientific Inc. and its subsidiaries. This information is presented as an example of the capabilities of Thermo Fisher Scientific Inc. products. It is not intended to encourage use of these products in any manner that might infringe the intellectual property rights of others. Specifications, terms and pricing are subject to change. Not all products are available in all countries. Please consult your local sales representative for details.

Africa +27 11 822 4120	Denmark +45 70 23 62 60	India +91 22 6742 9434	New Zealand +64 9 980 6700
Australia +61 3 9757 4300	Europe-Other +43 1 333 50 34 0	Italy +39 02 950 591	Russia/CIS +43 1 333 50 34 0
Austria +43 1 333 50 34 0	Finland/Norway/Sweden +46 8 556 468 00	Japan +81 45 453 9100	Spain +34 914 845 965
Belgium +32 53 73 42 41	France +33 1 60 92 48 00	Latin America +1 561 688 8700	Switzerland +41 61 716 77 00
Canada +1 800 530 8447	Germany +49 6103 408 1014	Middle East +43 1 333 50 34 0	UK +44 1442 233555
China +86 10 8419 3588		Netherlands +31 76 579 55 55	USA +1 800 532 4752

Thermo
SCIENTIFIC

Part of Thermo Fisher Scientific