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Probing the Reactivity of Dimethylsulfoxonium Methylide with Conjugated and Nonconjugated Carbonyl Compounds: An Undergraduate Experiment Combining Synthesis, Spectral Analysis, and Mechanistic Discovery

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Undergraduate organic laboratory experiments are often of an expository or verification type where students perform instructor-generated procedures merely to confirm a predetermined outcome *(1, 2)*; however, an increasing number of inquiry-driven (discovery-based, guided inquiry) *(3, 4)* experiments are being proposed where the procedure is instructor-generated but the outcome is not specified to the student *(5)*. In some cases, students are led to expect a particular outcome that does not occur, forcing them to reconcile experimental data that are inconsistent with the anticipated reaction product *(6)*. We report an operationally straightforward second-semester experiment of the latter type where students are introduced to the dimethylsulfoxonium methylide (DMSY) *(7, 8)* epoxidation of simple aldehydes and ketones, and *are left to discover for themselves that DMSY cyclopropanates α,β-unsaturated ketones (enones)* by a Michael-initiated ring closure (MIRC) reaction *(9, 10)* (Scheme 1).

The Experiment

This experiment was performed by students enrolled in several sections (8−20 students per section) of the second-semester introductory organic chemistry laboratory. A single 4-h lab period is sufficient for both the spectral analysis of the carbonyl substrate and its reaction with DMSY; the latter is formed in situ from reaction of trimethylsulfoxonium iodide (TMSOI) and potassium *t*-butoxide (KO*t*-Bu) in the presence of the carbonyl substrate *(11, 12)*. Product spectra are obtained either on the same day or during another lab period, or students are provided with copies of representative NMR and IR spectra. The experimental procedure is straightforward: typically, a DMSO solution of the carbonyl substrate (0.5−1.5 mmol) is added to a 25-mL Erlenmeyer flask containing an appropriate amount (1.2−3.0 molar equiv) of a dry, storable, equimolar mixture of TMSOI and KO*t*-Bu, and the resulting mixture is heated without stirring to approximately 60−70 °C for 30−45 min followed by treatment with brine and an extractive workup with an organic solvent. The reaction's progress can be easily monitored by TLC analysis. Complete experimental details for each substrate, student handouts, and full-scale spectral data are provided in the supporting information.

After a brief mechanistic discussion of the DMSY epoxidation of aryl and nonconjugated aldehydes and ketones, with no mention of the reagent's proclivity for conjugate addition, each student was asked to perform the reaction of DMSY with one of nine carbonyl compounds, of which four are enones (Figure 1). Before the experiment, students were provided with ^{1}H-decoupled ^{13}C NMR and IR[1] spectra of their assigned substrate, and a set of questions (Table 1) to answer independently and submit for instructor feedback.[2]

During either a second lab period or a lab lecture period, each student examined ^{1}H-decoupled ^{13}C NMR and IR spectra of their reaction product[3] along with their corrected answers to the first set of questions. They then answered, again on their own, a second set of questions (Table 1). The class as a group[4] then shared and compared results to draw general conclusions regarding the reactivity of DMSY toward the substrates examined. Another series of questions were provided to help focus group discussions on key spectral features (see the supporting information).

Hazards

Most carbonyl substrates and products are flammable, and all are irritants or harmful if inhaled or swallowed. Students should wear eye protection, a lab coat, and gloves. Trimethylsulfoxonium iodide may cause eye, skin, respiratory, and digestive tract irritation. Potassium *tert*-butoxide reacts violently with water and acids, possibly leading to fire, and is corrosive and extremely destructive of tissue of mucous membranes, respiratory tract, eyes, and skin. Dimethyl sulfoxide is a flammable liquid and causes irritation to the respiratory and gastrointestinal tract, skin, and eyes. It is readily absorbed through the skin and may result in the increased skin absorption of other more toxic materials. Dichloromethane is an eye and skin irritant and is readily absorbed through the skin. It causes CNS depression and is possibly carcinogenic in humans.

Results and Discussion

Product analysis by ^{1}H-decoupled ^{13}C NMR spectroscopy was chosen for this experiment because (i) it is generally easier than ^{1}H NMR for students to understand and interpret *(13)*; (ii) the success or failure of epoxide formation at the carbonyl carbon is easily established by the absence or presence of the characteristic downfield carbonyl peak (IR spectroscopy provides corroborative evidence);[1] and (iii) using the assumption that most sp^3 and sp^2 carbons resonate at $<\sim$100 ppm and $>\sim$100 ppm, respectively, reaction at the alkene functionality of enones is established

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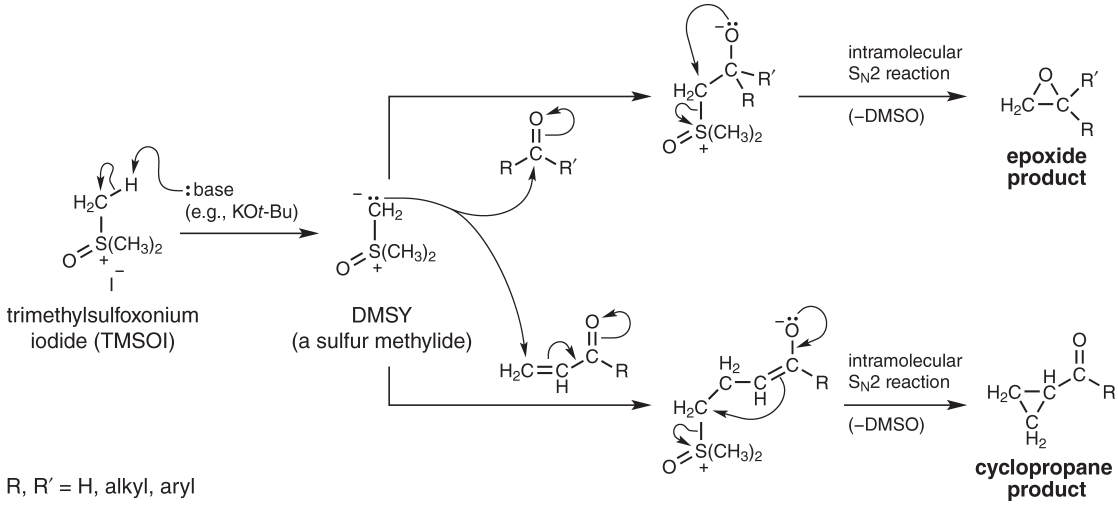
Scheme 1. Divergent Reactions of DMSY with Simple Carbonyl Compounds or Enones



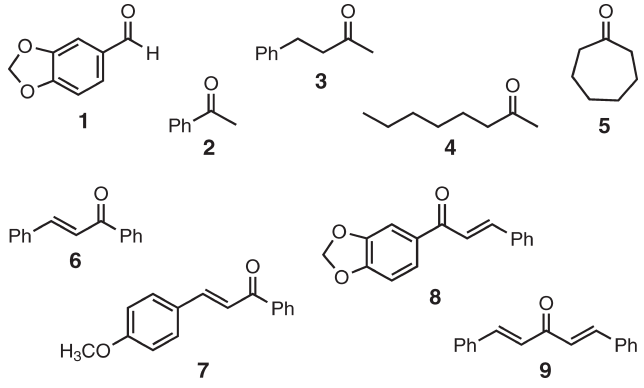


Figure 1. Carbonyl substrates for reaction with DMSY.

by comparing the expected versus actual number of peaks in the product's ^{13}C spectrum corresponding to sp^2 and sp^3 carbons.

Providing feedback to students about the spectral analysis of their carbonyl substrate and of their anticipated epoxide product ensured that everyone was on the right track before they proceeded with spectral analysis of their actual product. The questions students answered individually helped to focus their attention on key spectral features so that, during the group discussion, they could quickly see the inconsistencies between the spectral data of products from enones and that of products from the other substrates. With only a basic knowledge of ^{13}C NMR spectroscopy, all students, without exception, readily concluded that substrates **1**–**5** afforded the anticipated epoxides because the spectra of the corresponding products showed the expected absence of a carbonyl peak and the appearance of two new upfield peaks (indicating carbonyl epoxidation); however, ^{13}C NMR spectra of products from enones **6**–**8** unexpectedly (to the student) displayed a carbonyl peak, fewer than expected (sp^2 C) peaks at >∼100 ppm, and three (instead of the expected two) additional (sp^3 C) peaks at <∼100 ppm (Figure 2).

Either working on their own or in a group, none of the students could immediately identify the enone products as cyclopropanes, although all quickly realized that they were not epoxides, especially after they began to share and compare spectral data. After being asked to identify all electrophilic carbons in the enone structures by using charge-separated resonance structures *(14)*, most students realized that the nucleophilic methylide carbanion could attack the electrophilic β carbon of the enones; not surprisingly, this was more readily apparent to students familiar with the Michael reaction. With some further guidance, students eventually identified these products as cyclopropyl ketones, which led to a discussion of conjugate addition and MIRC reactions. The reaction of dibenzalacetone, **9**, with DMSY provided an excellent example of the facial stereotopicity of alkenes through formation of diastereomeric dicyclopropyl ketones, which caused the ^{13}C NMR spectrum of the product to

Table 1. Questions for Students

Part 1

What is the number of nonequivalent carbon sets in the chemical structure of your starting material, and which peaks in its ^{13}C NMR spectrum correspond to sp^3 (<∼100 ppm) and sp^2 (>∼100 ppm) carbons?

Draw the chemical structure of your anticipated reaction product: state the number of nonequivalent carbon sets present and the number of ^{13}C NMR peaks expected at <∼100 ppm (sp^3 C) and >∼100 ppm (sp^2 C).

State the expected differences between the spectra of your starting material versus your anticipated product, including the difference in the number of ^{13}C NMR peaks for sp^3 C and sp^2 C.

Part 2

Based on its ^{13}C NMR spectrum, what is the number of nonequivalent carbon sets in the chemical structure of your ACTUAL product, and which NMR peaks correspond to sp^2 C and sp^3 C? How do these numbers compare with your answer in Part 1?

Is the IR spectrum of your ACTUAL product consistent with the structure of the anticipated epoxide product (i.e., the presence or absence of what key spectral feature makes it either consistent or inconsistent)?

Make tentative chemical shift assignments if the number of ^{13}C NMR peaks in the spectrum of your ACTUAL product, and their ppm values, are consistent with the structure of the anticipated epoxide product; if they are not consistent, state the major discrepancies between the ACTUAL ^{13}C spectrum and the spectrum expected for the anticipated epoxide, including the expected versus observed number of ^{13}C NMR peaks for sp^3 C and sp^2 C.

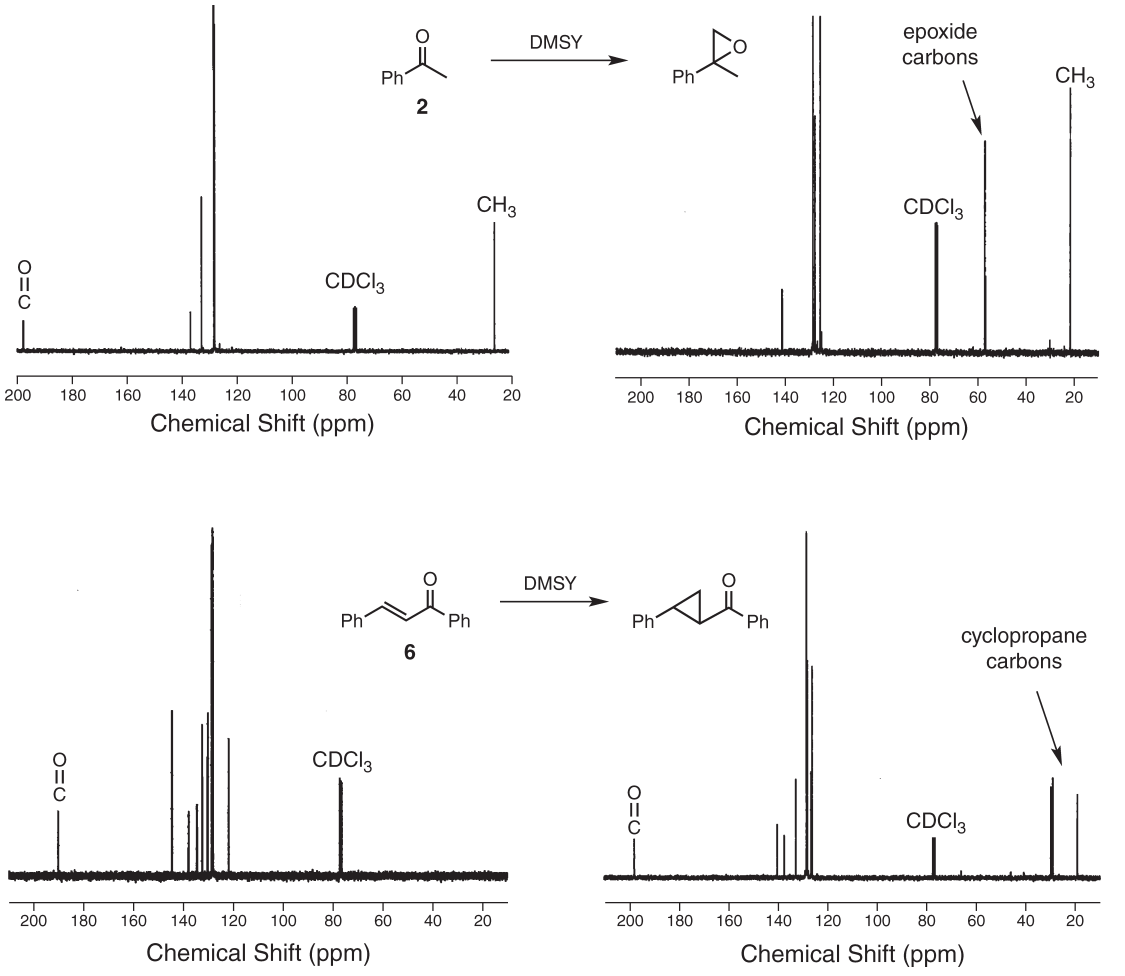


Figure 2. Comparison of substrate versus product ^{13}C NMR spectra for the DMSY reactions of acetophenone, **2**, and chalcone, **6**. When the epoxide region of the NMR spectrum for the product of **2** is expanded, the two peaks for the nonequivalent epoxide carbons are clearly seen (see the supporting information).

display twice the number of expected peaks in pairs that were <1 ppm apart. Usually at least one astute student in each section was able to explain this phenomenon on their own once they realized that the enones were undergoing cyclopropanation with DMSY.

Summary

This experiment stresses (i) the need to critically examine experimental data to avoid making false assumptions about the outcome of chemical reactions *(6)*; (ii) the necessity of investigating a variety of substrates to gauge the scope of a chemical reaction; (iii) the benefits of collaborative work; (iv) the ready preparation of epoxides by a method other than peroxy acid or alkaline hydrogen peroxide epoxidation of alkenes *(15)*; and (v) the synthetic use of an ylide containing a heteroatom other than phosphorus, and its striking difference in reactivity versus Wittig reagents toward carbonyl compounds *(9)*. Although at the outset of the experiment students do not realize it, reactions with DMSY are not performed merely for the sake of illustrating a known reaction; students must spectroscopically *analyze* their products to establish the correct structures, and they are left to discover for themselves the chemoselectivity of the reagent.

This experiment uses common glassware and commercially or readily available materials, and the reaction is run on a small scale, reducing costs and increasing lab safety. The "instant methylide" chemistry employed permits methylide formation in the presence of substrates, affords clean products in relatively short reaction times, and the mixture of TMSOI/KO*t*-Bu is stable and can be prepared and stored prior to use *(11, 12)*. Plausible extensions and variations of this experiment are possible and all would serve as meaningful exercises in spectral analysis and mechanistic problem solving.

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Notes

1. Students readily reached the same mechanistic conclusions using only ^{13}C NMR data, making IR spectroscopy optional for this experiment.
2. To save time, students can analyze their substrate's spectra and answer the first set of questions during the 30−40 min reaction time; alternatively, students can be provided with substrate spectra and related questions well in advance of the actual experiment.
3. Most students obtained >100 mg of product, making it possible for students in small lab sections to obtain spectra of their own

samples relatively quickly using a high-field FT-NMR spectrometer; to save time, copies of representative spectra could be distributed to the rest of the class.

4. Large lab sections were divided into small groups of four containing at least one student who was assigned an enone; for small sections, all students gathered around a blackboard to present and discuss their results.

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Supporting Information Available

Instructor notes; written material for the students; detailed safety information; spectra. This material is available via the Internet at http://pubs.acs.org.