Investigating a Reaction of *N*–Methyltriazolinedione

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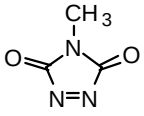
Abstract: This undergraduate laboratory experiment challenges students to use their combined knowledge of organic reaction mechanisms and spectroscopic analysis to determine the product of a reaction that has several possible outcomes. The result is that students gain the "real-life" experience, commonly encountered by most research chemists, of characterizing and identifying an unknown organic substance.

Introduction

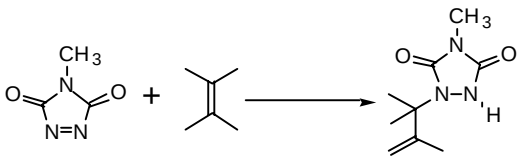
Research chemists are often faced with the task of characterizing and identifying an unknown compound obtained from a reaction. Usually several possible reaction products are scrutinized to determine whether their structures are compatible with obtained data. While this process can be somewhat exasperating at times, it often provides some of the most exciting times for a chemist because of the inherent challenges in elucidating the structure of an unknown substance. The following laboratory experiment attempts to simulate this unique experience with students in a laboratory setting. An experimental procedure is provided for the students to follow for the synthesis and isolation of a reaction product, but the ultimate identity of the product is left unknown for the students to deduce.

N-Methyl-1,2,4-triazoline-3,5-dione (MeTAD) is a strongly electrophilic azo compound



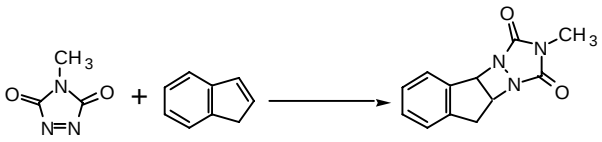
MeTAD

that readily engages in reactions with a variety of functional groups including alkenes, alcohols, ketones, and aromatics [1]. The outcome of the reaction of MeTAD with alkenes is intimately related to the structure of the chosen alkene [2]. Reaction with alkenes containing allylic hydrogens often affords ene-type products such as in the reaction of MeTAD with 2,3–dimethyl–2–butene (eq 1) [1–3].



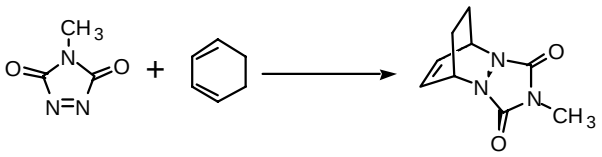
(1)

Reaction with alkenes lacking allylic hydrogens, as well as with some alkenes that do contain allylic hydrogens, can afford [2+2] adducts such as in the reaction of MeTAD with indene (eq 2) [1, 2, 4].



(2)

Finally, reaction of MeTAD with dienes that are able to undergo Diels–Alder cycloadditions can afford [4+2] adducts such as in the reaction of MeTAD with cyclohexadiene (eq 3) [1, 2].



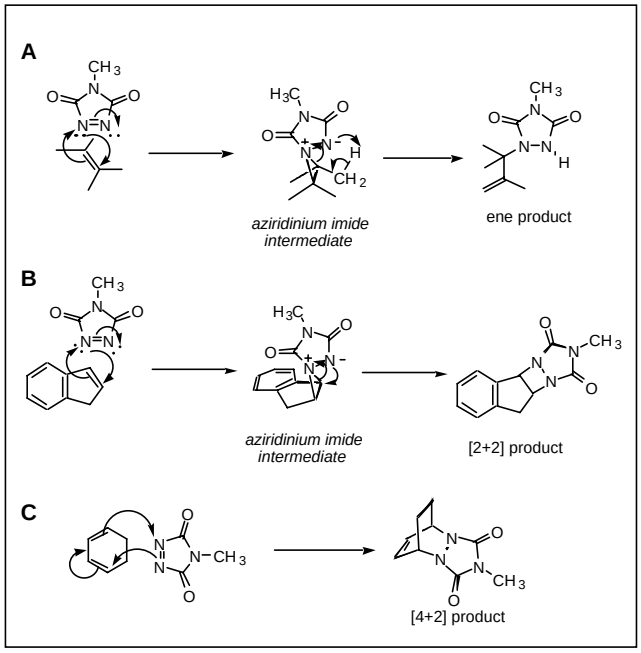
(3)

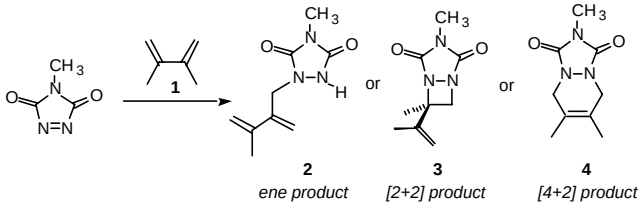
The ene reaction and the [2+2] cycloaddition take place via strained cyclic intermediates known as aziridinium imides (Scheme 1) [1, 2, 5, 6] Abstraction of an allylic proton by the negatively charged nitrogen atom of the intermediate affords an ene product (Scheme 1A), while attack by the negatively charged nitrogen atom at one of the two aziridine carbon atoms of the intermediate affords a [2+2] cycloadduct (Scheme 1B). The [4+2] adduct probably derives from a concerted reaction with MeTAD acting as a simple dienophile (Scheme 1C).

For this experiment 2,3-dimethyl-1,3-butadiene (**1**) was chosen as the alkene for study (eq 4). Because of the structure of **1**, its reaction with MeTAD provides the opportunity for all three avenues of reaction to yield any of three possible products **2**–**4** (eq 4). Only one of the three possible products is formed, however, and it is left to the student to properly assign its structure.

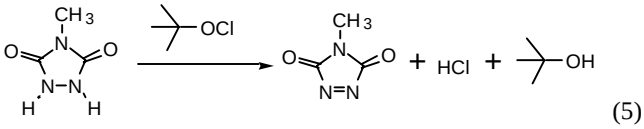
MeTAD is commercially available, but its cost is approximately five times that of its immediate precursor, *N*-methylurazole (eq 5). The oxidation of *N*-methylurazole to MeTAD is a facile process that can be carried out with *tert*-butylhypochlorite, which is easily made by the instructor prior to class (see Supplemental Information 44gb1897.pdf). The oxidation reaction is actually quite interesting itself as it is accompanied by a rather spectacular coloration of the reaction mixture because the starting urazole is colorless while MeTAD is deep red in color.

Scheme 1. Reaction mechanisms for formation of various types of products in the reactions of metad with alkenes.





(4)



(5)

Experimental

Materials. All compounds used in this experiment were purchased from Aldrich with the exception of tert-butylhypochlorite, which was freshly prepared by the instructor beforehand according to a literature procedure (see the Supplemental Information 44gb1897.pdf) [8]. Both tert-butylhypochlorite and MeTAD are light-sensitive compounds and should be protected from excessive ambient light when possible.

Safety Precautions. If possible, all manipulations should be carried out in an efficient hood. If, however, sufficient hood space is not available to accommodate all students for the entire experiment, one operational step that **must be** carried out in a hood is specified in the experimental procedure given below. tert-Butylhypochlorite is a toxic, noxious-smelling compound that should be dispensed only in the hood.

Instrumentation. Infrared analyses were performed on samples prepared as KBr pellets on a Perkin–Elmer 1700 series FT IR spectrophotometer. NMR spectra were obtained on solutions in $CDCl_3$ at 60 MHz (^1H), or at 15.1 MHz (^{13}C), on a Varian EM-360 that had been upgraded to FT capability (Anasazi Instruments Inc.).

Procedure [9]. *N*-Methylurazole (50 mg, 0.43 mmol) was weighed into a 3-mL conical vial. A stir bar was added along with 0.5 mL of EtOAc. A cap with septum was placed tightly on top, the cap edge was sealed with Parafilm, and the vial was set into an ice bath on top of a magnetic stirrer. Care was taken to not get water near the cap of the vial. After stirring for 5 minutes, the stirrer, ice bath, and vial assembly were transported to a fume hood (the lights in the hood were extinguished) where *tert*-butyl hypochlorite (45 μL, 0.9 equivalents) was added via syringe (through the septum of the cap) all at once to the stirring mixture. The mixture turned red shortly thereafter, signaling the production of MeTAD. The assembly was covered with a paper towel to block out excess irradiation by room lights, brought back to the workbench, and stirred for 15 minutes in the ice bath followed by stirring for 5 min at room temperature.

While stirring the MeTAD solution, a solution of 2,3-dimethyl-1,3-butadiene (43 mg, 1.2 equivalents) was prepared by weighing it directly into a clean 5-mL conical vial followed by the addition of 0.5 mL of EtOAc. A stir bar was added to the solution, and it was set on a stir plate.

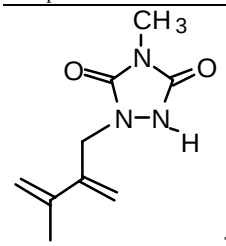
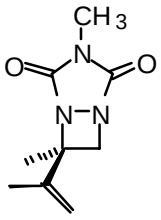
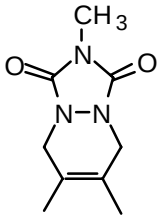
After stirring the MeTAD reaction mixture at room temperature for the specified time (the mixture was a slightly cloudy, deep red solution), it was filtered through a pipet containing a tight plug of glass wool supporting a short column of sand into a clean glass vial. The flask was rinsed with 2 × 0.5 mL of EtOAc, and each rinse was run through the filter pipet into the vial. Stirring was commenced in the vial containing the diene solution, and the filtered MeTAD solution was added **dropwise**. The red color of the MeTAD rapidly dissipated as the solution was added to the diene. The resulting mixture was stirred another 5 min and was then transferred with a pipet to a round-bottom flask, using methylene chloride (1–2 mL) to aid in the transfer. The solvent was removed via rotary evaporation to yield a solid. Methylene chloride (3 mL) was then added to the flask and the contents swirled well to dissolve all soluble material. Some material did not dissolve (primarily unreacted *N*-methylurazole). The methylene chloride solution was filtered through a second pipet containing a tight plug of glass wool supporting a short column of sand into a clean, tared, round-bottom flask. The flask and filter pipet were rinsed with methylene chloride (1 mL) into the flask, and the solvent again removed via rotary evaporation to afford a white solid in yields of approximately 90%, mp 170–171 °C (recrystallization from 95% EtOH afforded colorless needles but did not increase the melting point). ^1H NMR (60 MHz, $CDCl_3$, δ): 3.89 (br s, 4H), 3.08 (s, 3H), 1.75 (br s, 6H). ^{13}C NMR (15.1 MHz, $CDCl_3$, δ):152.6, 120.1, 46.9, 25.3, 16.3. IR (KBr, cm^{-1}): 2951, 2919, 1769, 1719 (C=O), 1462, 744.

Results and Discussion

At the beginning of the laboratory period, the three modes of reaction of MeTAD with the model alkenes (2,3-dimethyl-2-butene, indene, and 1,3-cyclohexadiene) were presented. Using the reaction mechanisms depicted in Scheme 1, the students were asked to predict the three possible reaction products (compounds **2**–**4**) that could be formed from reaction of MeTAD with diene **1**. The reaction was then carried out as described above, and the product characterized.

The product of the reaction may be definitively assigned using standard spectroscopic methods of analysis. The expected spectroscopic data for each of the three possible products are summarized in Table 1 (with comparison to the experimentally determined data). It is clear from this analysis that the observed reaction product must result from a [4+2] cycloaddition because it is the only product that matches the observed data from all three analytical methods. It is quite instructive for the students to complete this table for compounds **2**–**4** themselves, and observe firsthand the power of spectroscopic prediction for structure determination.

Table 1. Predicted Spectral Data for Possible Reaction Products 2–4 and the Observed Spectral Data for the Reaction Product

Compound	IR Data	^{1}H NMR Data	^{13}C NMR Data
 2	N–H stretch (~3500 cm^{-1}) Unsaturated C–H (~3010 cm^{-1}) Saturated C–H (~2950 cm^{-1}) Carbonyl (~1720 cm^{-1})	N–Me (~3 ppm) N–H (~10 ppm) Vinyl protons (~5–6 ppm) Allylic CH_2–N (~4 ppm) Allylic CH_3 (~2 ppm)	Total of nine carbon signals Two chemically inequivalent carbonyl carbons Four types of vinyl carbons
 3	Unsaturated C–H (~3010 cm^{-1}) Saturated C–H (~2950 cm^{-1}) Carbonyl (~1720 cm^{-1})	N–Me (~3 ppm) Vinyl protons (~5–6 ppm) CH_2–N signal (~2.5 ppm) Allylic CH_3 signal (~2 ppm) Non–allylic CH_3 (~1 ppm)	Total of nine carbon signals Two chemically inequivalent carbonyl carbons Two types of vinyl carbons
 4	Saturated C–H (~2950 cm^{-1}) Carbonyl (~1720 cm^{-1})	N–Me signal (~3 ppm) Allylic CH_2–N (~4 ppm) Allylic CH_3 (~2 ppm)	Total of five carbon signals One type of carbonyl carbon One type of vinyl carbon
Reaction Product	Saturated C–H (2951, 2919, 2849 cm^{-1}) Carbonyl (1719 cm^{-1})	N–Me (3.1 ppm) Allylic CH_2–N (~3.9 ppm) Allylic CH_3 (1.8 ppm)	Total of five carbon signals One type of carbonyl carbon One type of vinyl carbon

Because we currently possess a ^{13}C probe of relatively low sensitivity, the ^{13}C NMR spectrum was the result of a group effort. After the students ran their individual ^{1}H NMR and IR spectra and obtained the melting points for their compounds, the products were combined to produce one ^{13}C NMR sample of high concentration (in $CDCl_3$). Data were then collected and processed in the presence of the entire class, and copies of the spectrum distributed to the students for analysis.

Most students had little difficulty deciding upon the [4+2] cycloadduct as the reaction product. The students engaged in much discussion with each other during the lab as they collected the various spectra. Each new piece of spectroscopic evidence was scrutinized to determine its best match with one of the three possible reaction products. They were generally pleased to be able to corroborate or dismiss the structures of the possible products using spectroscopic data.

Conclusion

This laboratory experiment, suitable for a second-semester or an advanced organic class, provides students with a real-life experience in characterizing and identifying an unknown reaction product. Identifying the product requires assimilating information from several different spectroscopic methods. Successful structure assignment depends not only upon corroborating the structure of a single product, but also upon being able to use the spectroscopic information to eliminate potential structures as possibilities.

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