The Microscale Laboratory

edited by
R. David Crouch
Dickinson College
Carlisle, PA 17013-2896

Microscale Synthesis of a Diphenylisoxazoline by a 1,3-Dipolar Cycloaddition

William B. Martin, Laura J. Kateley,* Dawn C. Wiser, and Catherine A. Brummond
Department of Chemistry, Lake Forest College, Lake Forest, IL 60045; **kateley@lfc.edu*

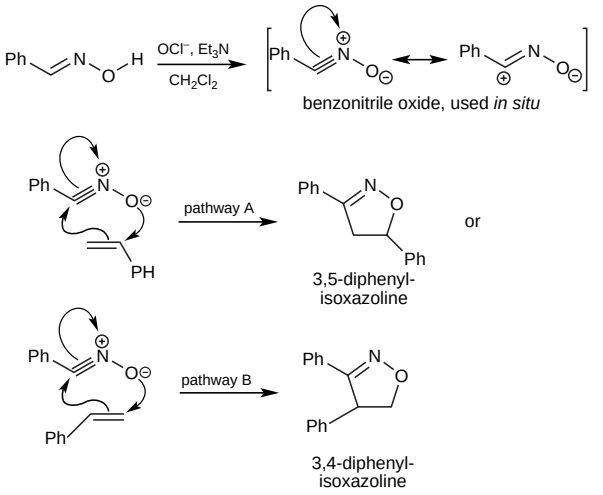
Background and Overview

Synthesis of a diphenylisoxazoline via a 1,3-dipolar concerted thermal cycloaddition reaction has been described by Lee (*1*) and adapted by Harwood, Moody, and Percy (*2*) for the undergraduate laboratory. In this experiment, the microscale synthesis has been modified. As presented here, two possible pathways are suggested, and the student uses NMR to identify the product and molecular modeling to explain the preferred pathway. The experiment is used in conjunction with second-semester organic chemistry lecture discussions of pericyclic reactions and heterocyclic chemistry. It provides experience with a pericyclic synthesis other than the analogous Diels–Alder reaction, and also a valuable application of ^{1}H NMR spectroscopy for determination of a structure with diastereotopic hydrogens exhibiting two-bond coupling. The learning experience is further enhanced by using molecular modeling. Geometry optimization of products and transition states provides information about thermodynamic and kinetic stability, respectively. Examination of frontier molecular orbitals leads to a better understanding of the significance of orbital overlap.

Huisgen was responsible for development of a large variety of heterocyclic syntheses using 1,3-dipoles and for recognition of these as examples of concerted cycloaddition reactions (*3*). Several monographs on alkene chemistry and 1,3-dipolar additions provide extensive information about these reactions (*4, 5*). Formation of an unstable molozonide when an alkene reacts with dipolar ozone is a familiar example of 1,3-dipolar addition. Organic chemistry texts by Eğe and by Carey and Sundberg discuss the scope of cycloaddition reactions using a variety of 1,3-dipolar molecules including ozone, phenyl azide, and nitrones (*6*, *7*).

These pericyclic reactions involve two reagents: the 1,3-dipole and an alkene or alkyne. The 1,3-dipole is termed such because of the contributing resonance form with formal positive and negative charges oriented 1,3 with respect to one another. Note that the 1,3 designation refers to relative positions of bonding atoms in the dipolar molecule and not to formal charges. The dipolar molecule contributes four electrons in the bond-making process: a pair of π electrons and a pair of nonbonding electrons from oxygen or nitrogen of the 1,3-dipole. Alkene or alkyne dipolarophiles contribute a pair of π electrons. Thus the reaction is described electronically as an allowed [4 + 2] cycloaddition in which the four π and two nonbonding electrons are in the ground state. Figure 1a shows the bonding HOMO and LUMO orbitals for this cycloaddition. Products are five-membered heterocycles with one or more nitrogen or oxygen hetero atoms.

In this experiment, the dipolarophile styrene reacts with the 1,3-dipolar benzonitrile oxide produced by hypochlorite oxidation of *syn*-benzaldehyde oxime. For this experiment, students are presented with a question regarding the structure of the product. Depending upon how the styrene is oriented with respect to the nitrile oxide when the 1,3-dipolar addition occurs, two possible products can be proposed. Thus, the product might be either 3,5-diphenylisoxazoline (pathway A) or 3,4-diphenylisoxazoline (pathway B).



Experimental and computational approaches are used to determine and substantiate the regioselectivity of the reaction. ^{1}H NMR is used to determine the regioselectivity of the reaction. Molecular modeling with MacSpartan Plus is used to understand the factors contributing to the observed regioselectivity.

Using version 2.0 ACD/HNMR simulator software, the following ^{1}H NMR chemical shifts are predicted: with the 3,5-diphenyl product, δ 3.5 for the diastereotopic methylene hydrogens, and δ 5.7 for the methine hydrogen; with the 3,4-diphenyl product, δ 5.1 for the diastereotopic methylene hydrogens, and δ 4.5 for the methine hydrogen. A limitation of the software is that it does not show that the diastereotopic hydrogens in these molecules are different and are coupled to one another. Chemical shift predictions may be given to the student if it is not feasible for them to use simulator software. Relative chemical shifts for methylene and methine hydrogens are what would be expected based on proximity to electronegative oxygen. In the actual high field ^{1}H NMR spectrum for the product, diastereotopic methylene hydrogens are at δ 3.4 and 3.8 and the methine hydrogen is at δ 5.7, which agrees well with values predicted for 3,5-diphenyl-

isoxazoline. All three hydrogens produce doublets of doublets. The explanation for these observed splittings for the hydrogens on the heterocyclic ring can be found in spectroscopy texts such as that by Pavia et al. or in the spectroscopy section of the organic chemistry text by Carey (*8, 9*).

Experimental Procedure

The following are added to a 10-mL Erlenmeyer flask: 1200 µL of CH_2Cl_2; 232 µL of styrene; 24 µL of triethylamine; 2000 µL of ~10% NaOCl. To the stirred, chilled mixture, 196 mg of *syn*-benzaldehyde oxime dissolved in 250 µL of CH_2Cl_2 is added slowly. Chilling and stirring are continued for 35–40 minutes.

The aqueous layer of the two-phase mixture is extracted with CH_2Cl_2. Combined organic layers are dried over anhydrous Na_2SO_4. The CH_2Cl_2 is evaporated with a stream of air.

Average student yield of crude product was 72% (48–97%). After recrystallization from 95% ethanol, average yield was 56% (42–74%). Our students do not obtain the melting points of their products. Lee reports mp 73–75 °C for the pure product (*1*).

^{1}H NMR Analysis

Students obtained ^{1}H NMR spectra of the diphenylisoxazoline in $CDCl_3$ with TMS on a high-field NMR spectrometer. Between δ 7 and 8 are overlapping signals for aromatic ring hydrogens, which are not useful for structure determination. Results of expansion and integration of the δ 3–6 region are as follows for hydrogens a–c:

a at C_4: δ 3.346, doublet of doublets, 1H, $^2J_{ab}$ = 16.4 Hz, $^3J_{ac}$ = 8.4 Hz
b at C_4: δ 3.783, doublet of doublets, 1H, $^2J_{ab}$ = 16.4 Hz, $^3J_{bc}$ = 11.2 Hz
c at C_5: δ 5.741, doublet of doublets, 1H, $^3J_{bc}$ = 11.2 Hz, $^3J_{ac}$ = 8.4 Hz

Hazards

Methylene chloride is toxic and carcinogenic. Styrene is a flammable, harmful irritant. Triethylamine is a flammable, corrosive lachrymator. *syn*-Benzaldehyde oxime is an irritant. Chloroform-D is a toxic irritant, carcinogenic, and mutagenic. Sodium hypochlorite, 10–13% available chlorine, is a corrosive oxidizing agent, causes burns, and releases toxic gas when acidified.

Molecular Modeling

Electronic and steric reasons for the observed regioselectivity in this 1,3-dipolar addition can be explored through molecular modeling. Using MacSpartan Plus, calculations are done for both the 3,4- and the 3,5-diphenylisoxazoline and for the transition states for each of the cycloaddition pathways. Depending on available time and level of student expertise, the modeling may be done by the students or demonstrated for them.

Results using structures from pathways A and B show that the 3,5-substituted product is 3.0 kcal/mol more stable than the 3,4-substituted product (geometry optimization at the HF/3-21G level). This energy difference can be attributed to an unfavorable steric interaction between the two phenyl rings on the 3,4-diphenylisoxazoline.

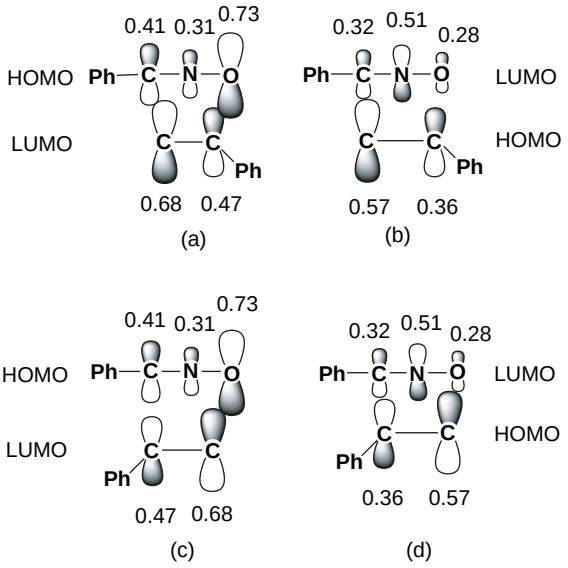


Figure 1. The most favorable frontier molecular orbital interactions involve the HOMO of the dipole and the LUMO of the dipolarophile. The magnitude of the coefficients favor the 3,5-diphenylisoxazoline. Schematic representations of the orbital approach to form the transition state leading to 3,5-diphenylisoxazoline are shown in (a) and (b). Schematic representations of the orbital approach to form the transition state leading to 3,4-diphenylisoxazoline are shown in (c) and (d).

Results from molecular modeling of the transition state structures show that the energy difference favors formation of the 3,5-diphenylisoxazoline by 3.7 kcal/mol (converged AM1 geometry, HF/3-21G single point energy calculation). Again, this energy difference can be attributed to the unfavorable steric interaction of the phenyl rings. Another pedagogically useful exercise based on the transition state calculation is to show the students the normal mode for the reaction coordinate, enabling them to see explicitly the changes occurring in the transition state.

Thus the molecular modeling results both for the products and for the transition states are consistent with observed product formation based on ^{1}H NMR analysis and provide support for the fact that only the 3,5 product is produced. Because both transition state modeling and product modeling predict the same product, the observed 1,3-dipolar addition is both thermodynamically and kinetically controlled.

Finally, as reported by Houk et al., analysis of the frontier molecular orbitals aids in further understanding the regioselectivity of the reaction (*11, 12*). Figure 1 illustrates the allowed overlaps for the HOMO and LUMO orbitals for the styrene dipolarophile and the nitrile oxide 1,3-dipole. Note that overlap of the HOMO of the dipole with the LUMO of the dipolarophile leads to a bonding interaction for both (Fig. 1, a and c), but the magnitudes of the coefficients favor the 3,5 product (Fig. 1a). Also note that for the formation of the 3,4 product to occur, the C atoms bonded to the phenyl rings will have to be close together to facilitate orbital overlap (Fig. 1c). This feat would be sterically difficult.

[w]Supplemental Material

Student handouts for synthesis and molecular modeling, notes for the instructor, an NMR spectrum, and figures showing electron density surfaces are available in this issue of *JCE Online*.

Literature Cited

1. Lee, G. A. *Synthesis* **1982,** 508.
2. Harwood, L. M.; Moody, C. J.; Percy, J. M. *Experimental Organic Chemistry*, 2nd ed.; Blackwell Science: Oxford, England, 1999.
3. Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963,** *2*, 565–598 and 633–645.
4. Huisgen, R.; Grashey, R.; Sauer, J. In *The Chemistry of Alkenes*, Vol. 1; Patai, S., Ed.; Wiley: New York, 1964; pp 806–878.
5. Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; pp 1–17. Caramella, P.; Grunanger, P. Ibid., pp 291–392.
6. Eğe, S. *Organic Chemistry: Structure and Reactivity*, 4th ed.; Houghton Mifflin: Boston, 1999; pp 1084–1088.
7. Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part A: Structure and Mechanisms*, 3rd ed.; Plenum: New York, 1990; pp 635–637.
8. Pavia, D. L.; Lampman, G. M.; Kriz, G. S. *Introduction to Organic Laboratory Techniques*, 3rd ed.; Harcourt College Publishers: Orlando, FL, 2001; pp 272–273.
9. Carey, F. A. *Organic Chemistry*, 4th ed.; McGraw-Hill: New York, 2000; pp 499, 507–508.
10. Moriya, O.; Nakamura, H.; Kageyama, T.; Urata, Y. *Tetrahedron Lett.* **1989,** *30*, 3987–3990.
11. Houk, K. N.; Sims J.; Duke, R. E. Jr.; Strozier, R. W.; George, J. K. *J. Am. Chem. Soc.* **1973,** *95*, 7287.
12. Houk, K. N.; Sims J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973,** *95*, 7301.