

Diels–Alder Synthesis of *endo-cis-N*-Phenylbicyclo[2.2.2]oct-5-en-2,3-dicarboximide

Marsha R. Baar* and Kristin Wustholz†

Department of Chemistry, Muhlenberg College, Allentown, PA 18104; *baar@muhlenberg.edu

The Diels–Alder reaction is an excellent illustration of an important carbon–carbon bond forming process that is also stereoselective. Many Diels–Alder reactions proceed readily at reasonable temperatures and in high yields, making them excellent candidates for an undergraduate organic chemistry lab experiment that reinforces key lecture concepts. If cyclic dienes are employed, then the stereoselectivity of the reaction, leading to *endo* products, can be observed (the Alder rule).

Most lab texts utilize 1,3-cyclopentadiene (**I**) as the cyclic diene because of its excellent reactivity and high yields with activated dienophiles at moderate temperatures. The typical dienophile is maleic anhydride (**II**), which is activated by its strong electron withdrawing anhydride group. Although this combination of diene and dienophile reacts within minutes and gives a high yield of *endo-cis*-bicyclo[2.2.2]oct-5-en-2,3-dicarboxylic anhydride (**III**, Figure 1), there are inherent problems associated with its use. The diene undergoes a Diels–Alder self-dimerization reaction to form dicyclopentadiene. It is the dimer that is commercially available and must be “cracked” by a time-consuming fractional distillation and then stored at low temperatures to prevent redimerization. Maleic anhydride is sold as hard briquettes, which must be pulverized. It is also moisture sensitive and inevitably hydrolysis products complicate the purification.

Literature Search

To overcome the problems associated with 1,3-cyclopentadiene and maleic anhydride, yet retain a system that illustrates the Alder rule, we investigated the reaction between 1,3-cyclohexadiene (**IV**) and *N*-phenylmaleimide (**V**). Pickering has suggested the use of 1,3-cyclohexadiene as the diene because it does not undergo the self-cycloaddition as readily as cyclopentadiene (*1*). Although it costs more than the dicyclopentadiene, it can be used directly and stored for months in a refrigerator without any appreciable dimerization. Also, as Pickering indicated, the reaction could be performed on microscale, to offset the higher cost. However, Pickering still utilized maleic anhydride as the dienophile, which required filtration of a pre-prepared anhydride/methylene chloride solution to remove maleic acid. Maleimide is the moisture resistant nitrogen analogue of the anhydride and the *N*-phenyl derivative was chosen in hopes of obtaining an insoluble product (**VI**, Figure 2) that would precipitate out of solution facilitating purification. The maleimide also comes as an easily dispensed yellow powder.

A literature search revealed that *endo-cis-N*-phenylbicyclo[2.2.2]oct-5-en-2,3-dicarboximide (**VI**) has been made previously by Diels–Alder cycloaddition (*2a–e*). Jimenez et al. performed the cycloaddition upon alumina without solvent. The dienophile was vigorously stirred, at 0 °C, with

K-10 montmorillonite (activated, but neutral aluminum oxide) until absorbed at which time the diene was added dropwise. The reaction mixture was stirred for 6 hours at 0 °C, conditions not well suited for the typical organic lab. Workup included extraction, filtration through Celite, evaporation, and recrystallization. The results were excellent; 86% of the *endo* cycloadduct was collected. Neither Jimenez et al., nor the other workers that described a Diels–Alder preparation of **VI**, provided physical properties for the cycloadduct. Unlike Jimenez et al., these other workers did not clearly identify experimental conditions, either.

The literature source that provided the melting point, IR, and ¹H NMR of **VI** was Hussein and Al-Kabi (*3*), but they prepared the desired cycloadduct by an alternate method. They utilized *endo-cis*-bicyclo[2.2.2]oct-5-en-2,3-dicarboxylic anhydride, whose *endo* configuration has been established by single crystal X-ray structure analysis, as their starting material. The anhydride group was converted into the *N*-phenylmaleimide by reaction with aniline in ether to form the amidoacid that was then dehydrated and cyclized with acetic anhydride and sodium acetate.

Reassured from the literature that the intended diene and dienophile do react to form the desired *endo* cycloadduct, which we could characterize, we turned our attention to determine conditions that shortened the reaction time and minimized the task of purification. The combination of 1,3-cyclohexadiene and *N*-phenylmaleimide are less reactive as a pair, especially when compared to 1,3-cyclopentadiene and maleic anhydride. At room temperature in ethyl acetate, 1,3-cyclopentadiene and maleic anhydride react exothermically within minutes yielding a precipitate of the cycloadduct. Pickering indicated that the switch to 1,3-cyclohexadiene in this reaction extended the time to 2 days. Obviously coupling the less reactive *N*-phenylmaleimide with the cyclohexadiene would further increase the reaction time at room temperature.

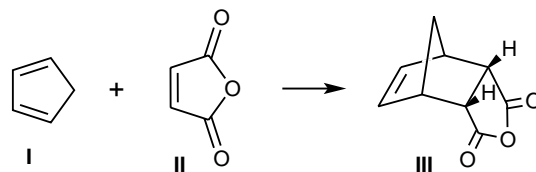


Figure 1. Cycloaddition of 1,3-cyclopentadiene (**I**) and maleic anhydride (**II**).

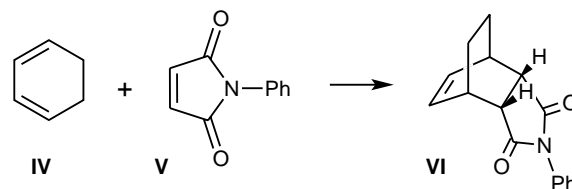


Figure 2. Cycloaddition of 1,3-cyclohexadiene (**IV**) and *N*-phenylmaleimide (**V**).

†Current address: Department of Chemistry, University of Washington, Seattle, WA 98195-1700

Hazards

1,3-Cyclohexadiene and ethyl acetate are flammable. Along with *N*-Phenylmaleimide they are also irritants. The spectral solvents, CHCl_3 and CDCl_3 , are toxic and cancer suspect agents, so gloves were worn and all operations were performed in the hood. Thermowells and powermites served as heat sources.

Results and Discussion

We were curious about how long the reaction between 1,3-cyclohexadiene and *N*-phenylmaleimide would take at room temperature, and whether the desired cycloadduct would precipitate directly from the reaction mixture. Utilizing the cyclopentadiene/anhydride reaction conditions, we stirred *N*-phenylmaleimide (yellow powder) and 1,3-cyclohexadiene (clear, colorless liquid) in ethyl acetate at room temperature (RT). All reagents initially dissolved, so the appearance of a white precipitate in an hour's time was encouraging. This solid was collected by suction filtration and analyzed by melting point (204–205 °C), IR (C=O stretch at 1708 and 1773 cm^{-1}), and ^1H and ^{13}C NMR and was found to be consistent with the desired cycloadduct, *endo-cis-N*-phenylbicyclo[2.2.2]-oct-5-en-2,3-dicarboximide (VI), but in a 15% yield.^{1,2} It was also deemed pure enough for student purposes.³

Encouraged by this result we set up a series of reactions, some at RT that were stopped after incremental 24-hour periods, and others that were refluxed and stopped after incremental 0.5-hour intervals. The reaction yield is 91% at RT in a week or under reflux in 2.5 hours.⁴ Thus an instructor may choose to have students synthesize and purify this Diels–Alder cycloadduct within one lab period by reflux or by allowing the reaction mixture to sit in student lockers for one week before filtration and analysis. The high melting point of the cycloadduct permits oven drying the same week for analysis. The 105 students who have performed this experiment with a shortened reflux time of 1.5 hours produced an average yield of 1.05 ± 0.10 g (78%) of shiny white crystals with an average melting point of 203.4–205.3 °C.⁵

The product was not only analyzed by its appearance and melting point, but by IR and ^1H and ^{13}C NMR spectroscopy. A more in-depth spectral analysis, in which both starting materials can be contrasted to product, is possible with our combination of diene and dienophile. In the original cycloaddition, 1,3-cyclopentadiene's instability prevented students from obtaining its spectral data. 1,3-Cyclohexadiene has characteristic IR and NMR peaks that are not present in the product's spectra. *N*-phenylmaleimide and the cycloadduct's IR spectra are almost identical, particularly in the functional group region, so this spectral method is not useful. However, their NMR spectra have unique peaks so it is possible to distinguish them.⁶ The cycloadduct's IR, ^1H and ^{13}C NMR spectra are included with the Supplemental Materials.^{u,7}

Summary

The increased stability of 1,3-cyclohexadiene and *N*-phenylmaleimide make them more “user-friendly” starting

materials, but their reduced reactivity does not preclude their use in a Diels–Alder reaction that illustrates the “endo” rule. The cycloaddition reaction can be performed on mini- or microscale, at room temperature or under reflux. The cycloadduct is formed in high yields without the assistance of catalysts or clays, readily precipitates out of solution, and is sufficiently pure as formed to eliminate the need for further purification. An additional educational benefit is the ability to spectrally compare starting materials to product. We are currently investigating microwave technology as another rate-enhancing method, which should allow the completion of the reaction and subsequent analyses within one lab period.

Notes

1. Hussein and Al-Kabi reported a melting point of 204–206 °C; IR C=O stretch at 1705 and 1765–1770 cm^{-1} ; ^1H NMR (400M Hz, CDCl_3 , δ): 1.51 (m, 4H, CH_2CH_2), 3.00 (s, 2H, =CHCH), 3.23 (s, 2H, $\text{CHC}=\text{O}$), 6.24 (q, 2H, $\text{CH}=\text{CH}$), 7.17–7.45 (m, 5H, N–Ph).

2. We repeated the synthesis of VI following Hussein and Al-Kabi's method. The product from their multistep sequence was identical to our cycloadduct by mp, mixed mp, IR, and ^1H and ^{13}C NMR.

3. Recrystallization from ethanol, 1 g/100 mL, improved mp to 206–207 °C.

4. A small quantity of cycloadduct remains in the filtrate. After 2.5 hours of reflux, the actual isolated quantity was 91.0%, but inclusion of filtrate portion increases yield to 98.6%. Further reflux did not improve the yield.

5. The only other solid was *N*-phenylmaleimide, which was yellow and melted at 85–87 °C.

6. IR and NMR spectra for all starting materials and ethyl acetate are available from Aldrich or at <http://www.aist.go.jp/RIODB/SDBS> (accessed May 2005).

7. We are the first reporters of the ^{13}C NMR spectrum of VI.

Acknowledgment

Kristin Wustholz's undergraduate summer research was supported by Barbara and Wilson Gum (Muhlenberg alumni-1961).

^uSupplemental Material

The student handout and report sheet, CAS numbers, and IR, 400 MHz ^1H and ^{13}C NMR spectra for *endo-cis-N*-phenylbicyclo-[2.2.2]-oct-5-en-2,3-dicarboximide (VI) are available in this issue of *JCE Online*.

Literature Cited

- Pickering, M. J. *Chem. Educ.* **1990**, *67*, 524–525.
- (a) Jimenez, J. L.; Avalos, M.; Babiano, R.; Bravo, J. L.; Cintas, P.; Palacios, J. C.; Ranu, B. C. *Tet. Lett.* **1998**, *39*, 2013–2016. (b) Pandey, B.; Athawale, A.; Reddy, R. *Chem. Lett.* **1991**, *7*, 1173. (c) Sauer, J. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 211. (d) Sauer, J. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 16. (e) Martin, J. G.; Hills, R. K. *Chem. Rev.* **1961**, *61*, 537.
- Hussein, F. A.; Al-Kabi, J. A. S. *Bull. Coll. Sci.* **1977**, *18*, 63–80.