

Multistep Synthesis of a Terphenyl Derivative Showcasing the Diels–Alder Reaction

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S Supporting Information

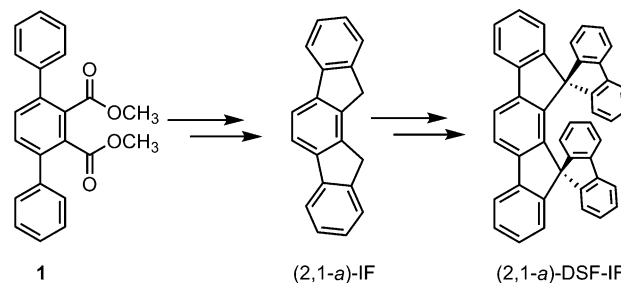
ABSTRACT: An adaptable multistep synthesis project designed for the culmination of a second-year organic chemistry laboratory course is described. The target compound is a terphenyl derivative that is an intermediate in the synthesis of compounds used in organic light-emitting devices. Students react a conjugated diene with dimethylacetylene dicarboxylate in a Diels–Alder reaction, then use enolate chemistry to isomerize and aromatize the adduct. Analysis of the synthesized intermediates and final compound is accomplished by thin-layer chromatography, NMR, and melting point. The synthesis can be expanded to four or five steps by linking to a previously published preparation of the diene. In addition to gaining experience with classic reactions in undergraduate organic chemistry courses, students are exposed to the utility of NMR spectroscopy by tracking subtle changes in the NMR spectra of structurally similar species.

KEYWORDS: Organic Chemistry, Second-Year Undergraduate, Laboratory Instruction, Hands-On Learning/Manipulatives, Synthesis, Elimination Reactions

Organic synthesis plays a significant role in the modern world; many pharmaceutical agents, cosmetics, and other useful materials are synthetically produced.¹ The process of organic synthesis is intricate, involving forethought regarding the reaction sequence, technical execution of experiments, analysis of reaction outcomes, purification of intermediates, and structural characterization. Moreover, the yield of each individual reaction must be high enough to produce adequate quantities of intermediate compounds to reach the target compound. Because organic synthesis requires the integration of many skills, it provides fertile ground for student learning and training.² The importance of organic synthesis to the undergraduate chemistry curriculum is articulated by the American Chemical Society (ACS) through its requirement that students carry out syntheses in ACS-accredited programs.³

Reported herein is an adaptable multistep synthesis of a terphenyl derivative designed as a capstone experience for a typical second-year organic chemistry laboratory course. The target compound (**1**, Scheme 1) has recently been reported⁴ as an intermediate in the synthesis of indenofluorene compounds under development for use in organic light-emitting devices (OLEDs), such as those found in digital displays (e.g., television screens, cell phones, tablet devices). In addition, terphenyl compounds have been employed in several chemistry subfields, such as medicinal chemistry,⁵ biosensor development,⁶ and materials science.⁷ The real-world applications of the synthetic target underscore the utility of organic synthesis and should capture student interest.

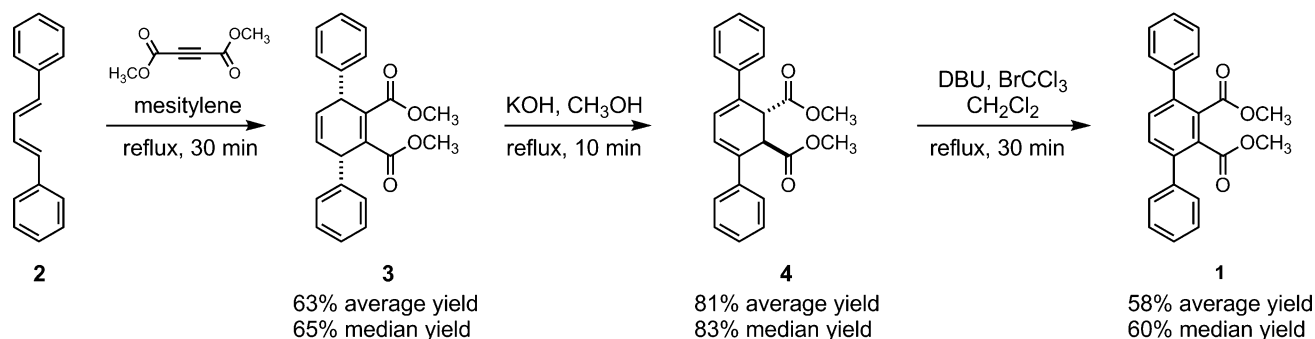
Scheme 1. Terphenyl Derivative 1 Is an Intermediate in the Synthesis of Two Compounds under Development for Use in Organic Light-Emitting Devices: (2,1-*a*)-IF, 11,12-Dihydroindeno[2,1-*a*]fluorene, and (2,1-*a*)-DSF-IF, Dispiro[fluorene-9,11'-indeno[2,1-*a*]fluorene-12',9''-fluorene]



OVERVIEW AND TIMELINE

The heart of this project involves a 3-step sequence that features chemistry typically emphasized in the introductory organic chemistry curriculum (Scheme 2). Conjugated diene **2** undergoes a Diels–Alder reaction with an alkyne; then adduct **3** is isomerized and aromatized to the final terphenyl product, **1**. The project was inspired by an experiment reported by John Lehman in his *Operational Organic Chemistry* textbook in which the diene is prepared and the use of it in a Diels–Alder reaction is mentioned, but not detailed.⁸ The steps shown in Scheme 2

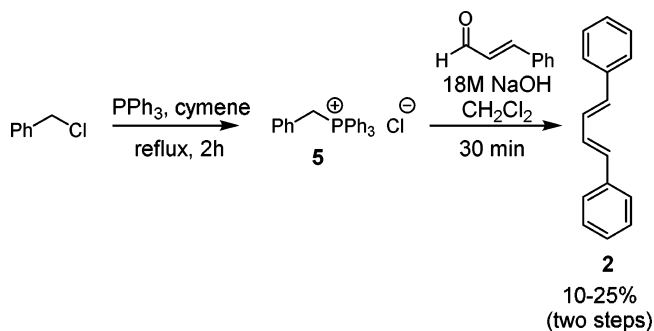
Scheme 2. Three-Step Sequence Developed To Produce Terphenyl 1



involve short reaction times such that the sequence can easily be accomplished over three 3-h lab sessions. Alternatively, these three steps have been successfully carried out over two lab sessions with access to the lab between sessions for analysis, in a more compact timeline.

The complexity of the project can be increased by linking to Lehman's 2-step diene preparation,⁸ which also uses chemistry classically featured in the introductory organic chemistry curriculum: S_N2 preparation of a phosphonium salt and a subsequent Wittig reaction (Scheme 3). When the diene

Scheme 3. Lehman's Two-Step Experiment⁸ for the Preparation of (*E,E*)-1,4-Diphenyl-1,3-butadiene (2). LEHMAN, JOHN W., OPERATIONAL ORGANIC CHEMISTRY, 4th edition, Copyright 2009. Reprinted by permission of Pearson Education, Inc., Upper Saddle River, NJ



synthesis is joined to the 3-step terphenyl production, a 5-step synthesis project can be carried out in four or five laboratory sessions, providing students with a rigorous multistep synthesis experience (see Table 1 for possible project timelines). In the spring of 2013, 10 pairs of students carried out the full 5-step project and all pairs successfully synthesized the final terphenyl product in 4 weeks following the most aggressive timeline (F). In 2015, 20 students successfully followed timeline A working individually (yields reported in Scheme 2) and 37 students made minor modifications to the procedures in attempt to optimize the overall process in a guided inquiry approach (see Supporting Information for conditions and results).

■ PEDAGOGICAL SIGNIFICANCE

This multistep synthesis project was designed to address several pedagogical goals for students: to deepen understanding of the Diels–Alder reaction and chemistry of the α carbon of carbonyl compounds, to hone their analytical skills through the analysis of intermediates, to gain experience with synthetic techniques

Table 1. Project Can Be Adapted To Be a 3, 4, or 5-Step Synthesis That Fits within Different Timelines, Depending on the Degree to Which the Instructor Wishes To Challenge Students and Incorporate Lehman's Diene Synthesis

Project timelines when purchasing diene 2	
A	week 1 - Diels–Alder reaction week 2 - isomerization of adduct week 3 - aromatization to 1
B	week 1 - Diels–Alder reaction AND isomerization week 2 - aromatization to 1
Project timelines when purchasing phosphonium salt 5 and linked to Lehman's synthesis of 2	
C	week 1 - Wittig synthesis of diene 2 (Lehman) week 2 - Diels–Alder reaction week 3 - isomerization of adduct week 4 - aromatization to 1
D	week 1 - Wittig synthesis of diene 2 (Lehman) week 2 - Diels–Alder reaction AND isomerization week 3 - aromatization to 1
Project timelines with full linkage to Lehman's synthesis of diene 2	
E	week 1 - phosphonium salt 5 synthesis (Lehman) week 2 - Wittig synthesis of diene 2 (Lehman) week 3 - Diels–Alder reaction week 4 - isomerization of adduct week 5 - aromatization to 1
F	week 1 - phosphonium salt 5 synthesis (Lehman) week 2 - Wittig synthesis of diene 2 (Lehman) week 3 - Diels–Alder reaction AND isomerization week 4 - aromatization to 1

and the challenges of carrying material through several reactions, and to master common calculations encountered in organic chemistry. Assessment of the goals was carried out after the project period by evaluation of formal lab reports and oral presentations.

First, the construction of the central aromatic ring of 1 is achieved through a Diels–Alder reaction, which plays a central role in the introductory organic chemistry curriculum.⁹ Whereas numerous one-step Diels–Alder experiments are published in the chemical education literature that particularly underscore *endo/exo* stereochemical outcomes,¹⁰ this project embeds the reaction within a sequence of steps showcasing the ring-forming synthetic power of the reaction. The fact that an alkyne is used as the dienophile in this Diels–Alder reaction removes the need to consider *endo/exo* diastereoselectivity, thereby allowing students to focus on the stereospecificity of the transformation as it relates to the geometry of the diene substituents. After the Diels–Alder reaction, the transformation

of **3** to **1** nicely illustrates a number of additional concepts central to introductory organic chemistry, namely reactivity at carbons alpha to a carbonyl, conjugation as a driving force in reactions, and the geometrical requirements of elimination mechanisms.

Throughout the project, students are challenged to provide evidence of the desired structural changes using a variety of analytical techniques, including TLC, NMR spectroscopy, and melting point determination. Because the chemical structure undergoes subtle yet distinct changes in the last two steps of the synthesis, student understanding of ^1H NMR features (e.g., splitting, chemical shift) is particularly strengthened through analysis and comparison of the ^1H NMR spectra of intermediates **3**, **4**, and the final product **1**.

Finally, the reactions in Scheme 2 work well on a relatively small scale, and students are encouraged to scale the procedures up or down depending on the amount of intermediates they obtain. This provides an excellent opportunity to practice and reinforce common organic chemistry calculations, including that of percent yield.

EXPERIMENT

Students work individually or in pairs to complete a multistep synthesis of a terphenyl derivative according to Schemes 2 and 3. Detailed procedures are provided in the Supporting Information. Students can also be grouped together and attempt to optimize the procedures in a guided inquiry fashion. The Supporting Information contains student results from minor modifications to the procedures.

HAZARDS

All experiments should be carried out in fume hoods and students should wear protective safety gear including goggles, gloves, and coats. Triphenylphosphine is a contact and inhalation irritant. Sodium hydroxide and potassium hydroxide are contact hazards and may cause burns. Dimethyl acetylenedicarboxylate is flammable, corrosive to the skin, and harmful to mucus membranes through inhalation. Mesitylene, *p*-cymene, petroleum ether, hexane, and ethyl acetate are flammable, contact and inhalation hazards, and potentially harmful to the central nervous system (hexane is a neurotoxin). Dichloromethane and chloroform-*d* are contact and inhalation irritants, and may be carcinogenic. Cinnamaldehyde is flammable and a contact and inhalation irritant. Benzyl chloride, methanol, and bromotrichloromethane are flammable, contact and inhalation irritants, and possible mutagens. To dispense bromotrichloromethane safely and in small quantities, a disposable syringe without a needle should be used. 1,8-Diazabicyclo[5.4.0]undec-7-ene is a contact and inhalation hazard, and may cause burns. The produced compounds are similar to *p*-terphenyl and should be treated as if they are contact and inhalation hazards, and toxic. Students should be cautioned about the use of any potential carcinogen or mutagen, and should take extra care when handling these chemicals as no level of exposure is considered safe. The heat source for all reactions carried out under reflux should be a heating mantle with variac; particular care should be taken when refluxing high-boiling organic solvents.

RESULTS AND DISCUSSION

Diene Synthesis

When (*E,E*)-1,4-diphenyl-1,3-butadiene (**2**) was prepared by students for the 5-step synthesis (timeline F), Lehman's diene procedure⁸ worked smoothly, although diene **2** was only obtained in 10–25% yield over two steps due to difficult recrystallization. Starting on a 35 mmol scale generated enough material to proceed successfully through the project. Alternatively, **5** can be purchased from several vendors for less than \$1/g to reduce the number of reactions in the project to four (timeline options C and D). Likewise, if timelines A or B are followed for a 3-step synthesis, **2** is available for less than \$3/g.

Diels–Alder Reaction

The Diels–Alder reaction of the diene with dimethylacetylene dicarboxylate (DMAD) is known to proceed in refluxing phenol,¹¹ in refluxing toluene for 12 h,⁴ or in toluene heated above the boiling point.¹² These procedures were modified for use in the undergraduate lab due to safety and time considerations. The use of a high-boiling aromatic solvent in combination with a high reaction concentration significantly reduced the reaction time. When a 1.5:1 ratio of DMAD to diene in refluxing mesitylene (2 M with respect to the diene) was used, the reaction was complete in 30 min. Because the reactants and product are UV-active, visualization by TLC was a convenient and instructive way to monitor the reaction. Upon cooling, the product (**3**) precipitated from the mixture and was isolated by vacuum filtration. The average student yield was 63%. The success of the crystallization had the greatest impact on the yield; students reporting lower yields generally performed less effective crystallizations.

Comparison of the product ^1H NMR spectrum to that of the starting diene clearly showed the incorporation of the methyl ester moiety into the product by the presence of a singlet at 3.56 ppm. The alkene proton signal was distinct from the aromatic region, represented by a doublet at 5.78 ppm (Figure 1, H_a). The benzylic proton environment was represented by a

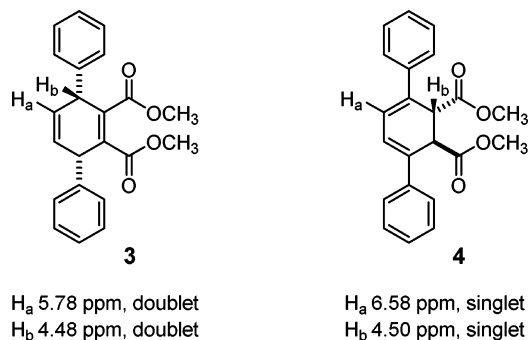


Figure 1. Structure and key ^1H NMR signals for similar protons in **3** and **4**.

doublet at 4.48 ppm (Figure 1, H_b). Since this signal is significantly farther downfield than a student would predict using a correlation chart (typically predicted to be 2.2–2.8 ppm), it provided an opportunity to emphasize the additive effect that two or more functional groups have on chemical shift.

Diene Isomerization

Aromatization of Diels–Alder adduct **3** was achieved in two steps, the first of which was base-catalyzed isomerization to

yield cyclohexadiene **4**. This known reaction¹³ was straightforward for students to perform; it required refluxing the adduct in a solution of KOH in methanol for 10 min. The reaction mixture was heterogeneous throughout the process, allowing the product (**4**) to be isolated by vacuum filtration as a solid in good yield (average of 81% yield).

The ¹H NMR of the product (**4**) was similar to that of the Diels–Alder adduct (**3**), but key differences were noted with respect to the alkene and allylic proton signals (Figure 1). First, both of these proton signals appeared as singlets because the change in structure resulted in a loss of neighboring protons. Second, the chemical shift of the alkene proton signal, H_a, was significantly shifted downfield to 6.58 ppm. The observed chemical shift is consistent with shielding prediction models¹⁴ for a vinyl proton bearing conjugated substituents similar to those present in **4**. (The predicted chemical shift is 6.79 ppm for a vinyl proton with a *gem* conjugated alkene, *cis* aromatic ring, and *trans* CH₂–C(O)R.)

Aromatization

Dehydrogenation of conjugated cyclohexadiene **4** was completed using a base-promoted bromination/elimination sequence. This type of aromatization has been reported to occur¹⁵ when a dihydro precursor is treated with 1,5-diazabicyclo[5.4.0]undecane (DBU) and bromotrichloromethane (1.1 equiv of each) in dichloromethane at 0 °C for several hours. The procedure was modified to fit into a 3 h laboratory period by adjusting the molar ratio of the reagents and conducting the reaction at elevated temperature. Students purified the terphenyl product by trituration and collected the product by vacuum filtration with an average yield of 58%. Analysis by ¹H NMR spectroscopy confirmed the formation of the terphenyl product because the spectrum lacked non-aromatic alkene proton signals (observed in the NMR spectrum of **4**) while still displaying a singlet for the methyl esters and a multiplet in the aromatic region.

SUMMARY

A flexible multistep synthesis of a useful terphenyl compound has been developed. In the project, students conducted a Diels–Alder reaction of a conjugated diene and alkyne, and then converted the adduct to the final product through two more steps involving enolate chemistry. The synthesis can be expanded to encompass the synthesis of the diene for an overall 5-step sequence, providing a capstone experience to an introductory organic laboratory class. Students completed pre-lab assignments every week and prepared lab reports and oral presentations at the end of the project. Most of the reports displayed increased knowledge of the classic reactivity involved in the reactions through well-developed introductions. The greatest student learning appeared to come from analysis of intermediates and the target compound by TLC, melting point, and most significantly by ¹H NMR spectroscopy through which the relationship of structure and chemical shift and splitting patterns was revealed.

ASSOCIATED CONTENT

Supporting Information

Included are procedures for students, pre-lab exercises with separate solutions, notes for instructors regarding possible modifications, student-acquired NMR spectra, melting point data, and TLC results for the Diels–Alder reaction. This

material is available via the Internet at <http://pubs.acs.org>. This material is available via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Assumption College is acknowledged for financial support of this work. Brian Niece is thanked for helpful discussions. Reviewers of the manuscript are thanked for insightful comments and suggestions.

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