ORGANIC

UNDERGRADUATE EXPERIMENT

Multistep Synthesis of Substituted *p*-terphenyl Derivative

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Introduction

Organic synthesis is crucial for the production of a wide array of products such as pharmaceuticals, fine chemicals, and synthetic materials that are vital to the modern world.[1] These syntheses typically require different skills such as planning the reaction sequence, execution of the reactions, isolation and purification, and analysis of the intermed ates and final product. NMR spectroscopy is highly complementary to organic syntheses due to its powerful structural elucidation capabilities. As such, laboratory experiences that enhance such skills should be incorporated into the undergraduate curriculum. In this app note, a multistep organic synthesis, adapted from a Journal of Chemical Education article published by Davie,[2] is performed and the intermediates and final product characterized and analyzed by ^{1}H NMR spectroscopy using the NMReady-60e.

The key reaction in this synthetic sequence is the Diels-Alder reaction.[3] First described by Otto Diels and Kurt Alder in 1928, a substituted cyclohexene derivative is formed in one step upon reaction of a conjugated diene and a dienophile (typically alkenes or alkynes) with a high degree of regio- and stereoselectivity. The reaction is a con certed process and believed to proceed via a single, cyclic transition state upon overlap of the highest occupied molecular orbital of the diene and the lowest unoccupied molecular orbital of the dienophile (figure 1).[3]

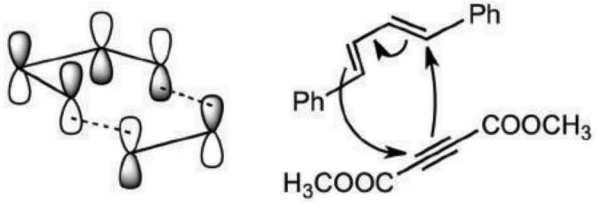
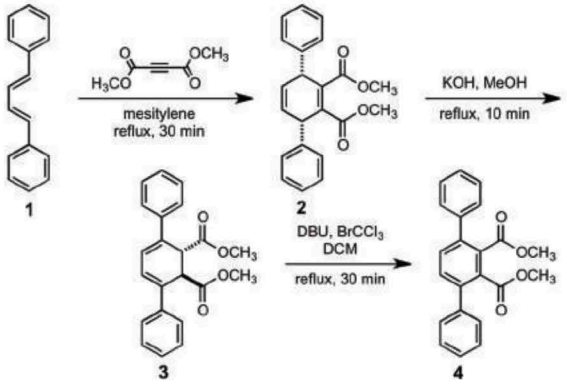


Figure 1. Left: Molecular orbitals involved in the Diels-Alder reaction. **Right:** Flow of electrons in the Diels-Alder reaction.

Synthetic Route



Scheme 1. Synthesis of terphenyl derivative **4**.

The terphenyl derivative **4** was synthesized in three steps starting from diene **1**. In the first step, compound **1** underwent a Diels-Alder reaction with dimethyl acetylenedicarboxylate to furnish **2** and form the six-membered ring at the core of the target compound. Subsequently, **2** is isomerized to **3** under basic conditions and then aromatized to give the final product **4**. If desired, **1** can be synthesized via a Wittig reaction to add another synthetic step to the reaction sequence.[2]

Procedure

Diene **1** (1.24 g, 6.00 mmol) was added to a round bottom flask and dissolved in 3.0 mL of mesitylene. Dimethyl acetylenedicarboxylate (1.1 mL, 9.0 mmol) was added and the mixture was heated to reflux for 30 min. Afterwards the flask was chilled in an ice bath and 2 mL of cold 95% ethanol was added. The recrystallized material was collected via filtration and washed with a small amount of cold 95% ethanol and dried to furnish **2** as a white solid in 66.6% yield (1.38 g, 3.97 mmol).

Compound **2** (1.05 g, 3.01 mmol) was added to a round bottom flask containing 0.15 M KOH in ethanol and the reaction was heated to reflux for 10 min. The isomerized product was recrystallized by cooling the flask in an ice bath and collected by filtration. The white crystals were washed with ice cold methanol to yield **3** (0.96 g, 2.76 mmol).

Compound **3** (0.35 g, 1.00 mmol) was added to a round bottom flask and dissolved in dichloromethane (5.0 mL). 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.38 mL) and bromotrichloromethane (0.22 mL) were added and the reaction was heated to reflux for 30 min. Subsequently, 20 mL of dichloromethane and 20 mL of a saturated ammonium chloride solution was added and mixed. The aqueous layer was separated from the organic layer and washed twice more with 20 mL of dichloromethane. The organic layers were combined, dried with $MgSO_4$, and the solvent removed on the rotary evaporator. Cold 95% ethanol (20 mL) was added to the residual solid which was collected via filtration, washed with cold 95% ethanol, and dried to give **4** as a white solid (88.0%, 0.304 g, 0.878 mmol).

Results & Discussion

Despite the subtle changes in the chemical structure between compounds **2**, **3**, and **4**, analysis and comparison of the ^{1}H NMR spectra allows for concrete assignment. The ^{1}H NMR spectrum of **2** (figure 2) displayed a singlet at 3.55 ppm that is indicative of the methyl ester moiety. The doublets at 4.47 ($^3J_{H-H}$ = 1.7 Hz) and 5.79 ($^3J_{H-H}$ = 1.8 Hz) ppm are assigned to the benzylic proton and alkene proton, respectively. The proximity of the two protons allows them to couple to each other, resulting in the observed doublets. Finally, the aromatic protons are found at 7.29 ppm.

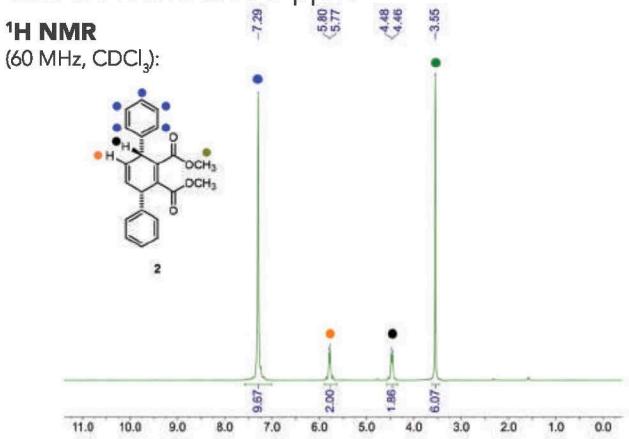


Figure 2. ^{1}H NMR spectrum of **2**.

The ^{1}H NMR spectrum of **3** (figure 3) is similar to that of isomer **2**, with a singlet at 3.58 ppm for the methyl ester protons and a multiplet at 7.38 ppm for the aromatic protons. A key difference is that both the allylic (4.48 ppm) and alkene (6.56 ppm) proton signals are present as singlets due to the change in the chemical structure as the protons are no longer neighbouring each other. Another significant change is the downfield shift of the alkene proton due to the conjugated system present in **3**.

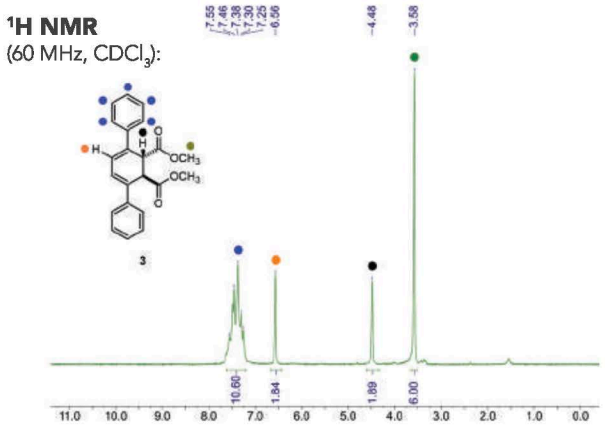


Figure 3. ^{1}H NMR spectrum of **3**.

Formation of the final terphenyl derivative **4** was confirmed by analysis of its ^{1}H NMR spectrum (figure 4). While signals for the methyl ester (3.58 ppm) and aromatic protons (7.37 ppm) are still present, the signal for the allylic proton has disappeared as expected after the dehydrogenation reaction. As well, the alkene proton signal has vanished upon aromatization of the central and are now present at 7.48 ppm.

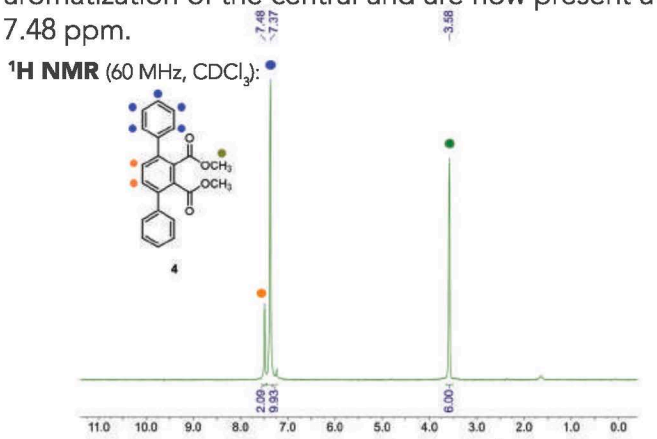


Figure 4. ^{1}H NMR spectrum of **4**.

Conclusions

In this experiment the three-step synthesis of terphenyl derivative **4** was accomplished utilizing the Diels-Alder reaction as the key reaction in the sequence, followed by an isomerization and aromatization reaction. The chemical structures of the intermediates and final product were then confirmed by analysing and comparing their ^{1}H NMR spectra. The series of ^{1}H NMR spectra obtained presents an excellent opportunity to discuss and reinforce key concepts in NMR spectroscopy.

References

[1]Nicolaou, K. C.; Sorensen, E. J.; Winssinger, N. *J. Chem. Ed.* **1998**, *75*, 1225-1258.
[2]Davie, E. A. C. *J. Chem. Ed.* **2015**, *92*, 1209-1213.
[3]Wade, L. G. Organic Chemistry, 8th ed.; Pearson: Boston, MA, **2012**; pp 684-693

Data Accessibility

The data can be processed directly on the NMReady-60 and printed and/or exported directly to a USB or networked file where it can be worked up using third party NMR processing software.