

The Arylnaphthalene Lactones Tale: Two NMR Spectroscopy Case Studies on the Surprises of a Dehydro-Diels–Alder Reaction.

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Instructor's Supplementary Information

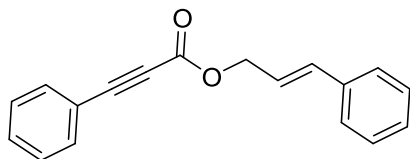
General. All reagents and solvents were purchased from Sigma-Aldrich and used without further purification. All NMR spectra were recorded on a Bruker Avance III 400 MHz or a Bruker Avance III 500 MHz spectrometer and were referenced to the residual chloroform (CDCl_3) resonance at 7.26 ppm for proton and 77.16 ppm for carbon. All cyclization reactions were performed on a 6 mL scale using ethanol as a solvent in an Anton Parr Monowave 50 oven at 140 °C in a 10 mL capped vial fitted with a magnetic stir bar. All chromatography separations were performed on a Teledyne Combiflash system using ethyl acetate/hexanes mixtures as eluent. IR spectra were recorded on a PerkinElmer UATR-Two Fourier Transform spectrometer. The high-resolution mass spectra were recorded in positive ion-mode with an ESI ion source on an Agilent™ Time-of-Flight LC/MS mass spectrometer Model 6210.

Typical Esterification Procedure.

To a flame-dried 5 mL two-necked round bottom flask equipped with an argon inlet adapter, a septum, and a stir bar were added the acid (2.05 mmol, 1 equiv.) and 4- dimethylaminopyridine (0.15 mmol, 0.07 equiv.), solution of cinnamyl alcohol (1.85 mmol, 0.9 equiv.) in dichloromethane (DCM, 10 mL) and N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDCI, 2.46 mmol, 1.2 equiv.). The reaction mixture was stirred at room temperature for 3 hours, diluted with DCM (15 mL) followed by a filtration through a plug of silica gel (3 cm plug using a Pyrex 15 mL frit funnel No. 36060 with 20 mm diameter and medium porosity). The crude material was subsequently concentrated under reduced pressure to yield the desired ester.

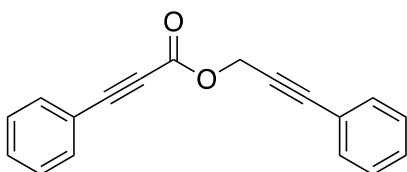
Note: Should the crude NMR show traces of either starting material or coupling agent, the crude was simply dissolved in DCM (10 mL) and filtered one more through another silica gel plug. This second filtration generally yielded high grade material suitable for subsequent step without further purification.

***trans*-Cinnamyl 3-phenylpropiolate**



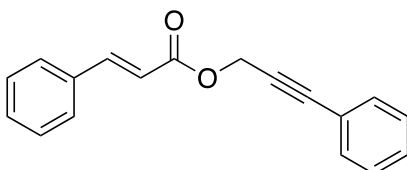
Isolated as a clear oil in 72% yield. Spectral data are in accordance with the literature.^[1] ¹H NMR (400 MHz, CDCl₃) δ = 7.66 – 7.59 (m, 2H), 7.51 – 7.27 (m, 8H), 6.76 (d, *J* = 15.9 Hz, 1H), 6.37 (dt, *J* = 15.9, 6.6 Hz, 1H), 4.92 (dd, *J* = 6.6, 1.2 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ = 154.0, 136.1, 135.5, 133.1, 130.8, 128.8, 128.7, 128.4, 126.8, 122.21, 119.7, 86.8, 80.6, 66.7 ppm.

3-Phenylprop-2-yn-1-yl 3-phenylpropiolate



Isolated as a yellow solid in 80% yield, mp: 48-52 °C. Spectral data are in accordance with the literature.^[2] ¹H NMR (400 MHz, CDCl₃) δ = 7.63 – 7.57 (m, 2H), 7.50 – 7.43 (m, 3H), 7.42 – 7.27 (m, 5H), 5.07 (s, 2H). ¹³C NMR (101 MHz, CDCl₃) δ = 153.4, 133.4, 132.1, 131.0, 129.1, 128.8, 128.5, 122.1, 119.6, 87.6, 87.5, 82.1, 80.2, 54.3 ppm.

3-phenylprop-2-yn-1-yl cinnamate

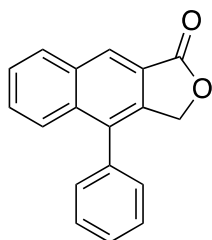


Isolated as a light yellow solid mp: 50-53 °C.^[3] ¹H NMR (400 MHz, CDCl₃) δ = 7.80 (d, *J* = 16.0 Hz, 1H), 7.62 – 7.53 (m, 2H), 7.54 – 7.47 (m, 2H), 7.45 – 7.39 (m, 2H), 7.39 – 7.32 (m, 3H), 6.53 (d, *J* = 16.0 Hz, 1H), 5.08 (s, 2H) ppm. ¹³C NMR (101 MHz, CDCl₃) δ = 166.2, 145.8, 134.3, 131.9, 130.5, 128.9, 128.8, 128.3, 122.2, 117.3, 86.6, 83.1, 52.9 ppm.

4-Phenylnaphtho[2,3-c]furan-1(3H)-one and 9-Phenylnaphtho[2,3-c]furan-1(3H)-one

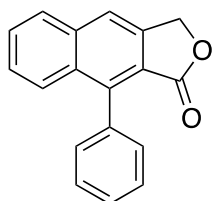
preparation. 3-Phenylprop-2-yn-1-yl 3-phenylpropiolate (150 mg) was dissolved in ethanol (6 mL) and the solution was irradiated in an Anton Parr Monowave 50 oven at 140 °C for one hour with constant stirring. After irradiation, the ethanol was removed under vacuum and the reaction mixture was purified using a Teledyne Combiflash system using ethyl acetate/hexanes mixture as eluent to yield two fractions containing 9-phenylnaphtho[2,3-c]furan-1(3H)-one (*R_f* = 0.20, 15% ethyl acetate/hexanes – silica gel) and 4-phenylnaphtho[2,3-c]furan-1(3H)-one (*R_f* = 0.40, 15% ethyl acetate/hexanes, silica gel).

4-Phenylnaphtho[2,3-c]furan-1(3H)-one



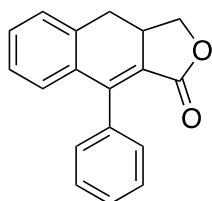
Isolated as a white solid, mp: 158–160 °C.^[2] ¹H NMR (400 MHz, CDCl₃): 8.52 (s, 1H), 8.09 (d, 1H, *J* = 7.03 Hz), 7.81 (d, 1H, *J* = 7.03 Hz), 7.62–7.51 (m, 5H), 7.39 (d, 2H, *J* = 6.64 Hz), 5.27 (s, 2H) ppm; ¹³C NMR (101 MHz, CDCl₃): 171.3, 138.6, 136.0, 135.0, 134.3, 133.9, 130.3, 129.5, 129.2, 129.2, 128.6, 126.9, 126.6, 126.1, 123.2, 69.7.

9-Phenylnaphtho[2,3-c]furan-1(3H)-one



Isolated as a white solid, mp: 174–176 °C.^[2] ¹H NMR (400 MHz, CDCl₃): 7.96 (d, 1H, *J* = 8.30 Hz), 7.90 (s, 1H), 7.81 (d, 1H, *J* = 8.79 Hz), 7.64 (t, 1H, *J* = 7.32 Hz), 7.54–7.52 (m, 2H), 7.48 (t, 1H, *J* = 7.32 Hz), 7.39–7.37 (m, 2H), 5.45 (s, 2H) ppm; ¹³C NMR (101 MHz, CDCl₃): 169.7, 142.4, 140.3, 136.4, 134.6, 133.0, 130.2, 128.8, 128.4, 128.3, 128.2, 128.2, 126.9, 120.4, 120.1, 68.3.

3a,4-Dihydro-9-phenylnaphtho[2,3-c]furan-1(3H)-one. *trans*-Cinnamyl 3-phenylpropionate (150 mg) was dissolved in ethanol (6 mL) and the solution was irradiated in an Anton Parr Monowave 50 at 140 °C for one hour with constant stirring. After irradiation, the ethanol solution was cooled to room temperature during which time the lactone started crystallizing as needles that were isolated by filtration.^[4]

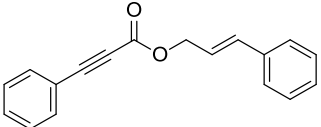
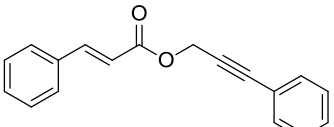
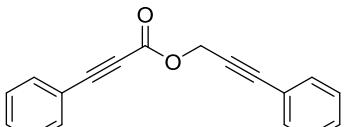


Isolated as a white solid, mp: 183–186 °C. ¹H NMR (400 MHz, CD₂Cl₂) δ = 7.46–7.43 (m, 3H), 7.33–7.26 (m, 4H), 7.19–7.15 (m, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 4.72 (t, *J* = 8.8 Hz, 1H), 4.04 (t (dd), *J* = 8.8 Hz, 1H), 3.50–3.40 (m, 1H), 3.07 (dd, *J* = 6.6, 15.0 Hz, 1H), 2.88 (t, *J* = 15.4 Hz, 1H) ppm. ¹³C NMR (101 MHz, CD₂Cl₂) δ 168.6, 147.2, 136.3, 136.1, 135.2, 130.2, 128.7, 128.5, 128.2, 127.5, 122.9, 71.7, 36.0, 33.2. ppm.

Differential Scanning Calorimetry (DSC) Analysis.

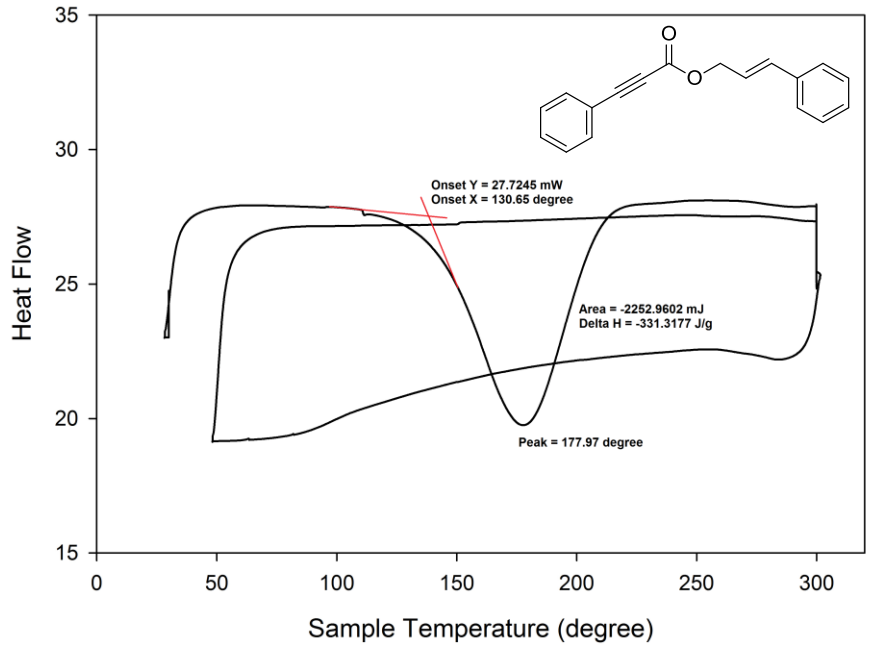
In the collected DSC, the temperature of the sample was increased linearly with time and the energy required was measured. In the sample with a constant heat capacity, a constant amount of energy will result in a linear increase in temperature. The cyclization (DDA) reactions for all three esters were found to be exothermic reaction, requiring no extra external heating and resulting in a negative peak.

DSC Procedure. All DSCs were carried out in the flow of nitrogen on a Perkin Elmer DSC 60000 with an auto-sampler. Samples were heated at a rate of 10 °C/min in alumina pans. Data were collected from 50 to 300 °C and cycled twice. All the onset temperatures and Enthalpy values are summarized in the table below, followed by all the data graphs.

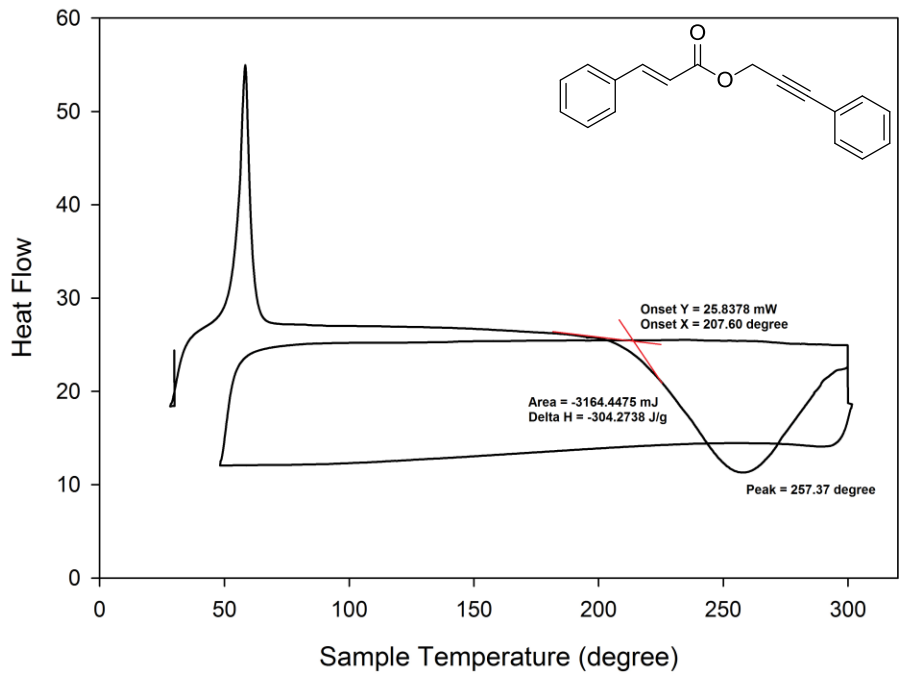
Compounds	T Final (°C)	T Initial (°C)	Scan Rate (°C/min)	Sample weight (mg)	Onset (°C)	Δ H (Area, J/g)
 Ester 1	300	50	10	6.8	130.65	-331.3177
 Ester 2	300	50	10	10.4	207.60	-304.2738
 Ester 3	300	50	10	16.2	125.88	-1066.8267

Note to the Grading Instructors. To avoid a multiplication of solutions to grade, we suggest to assign a letter or a number to each NMR signal (*or group of NMR signals*) and allow the students to assign those numbers or letters to the structures they report. Similarly, if the problem is a simple NMR signals' assignment and the structure is given, it is advised to provide the students with labelled structures (*all carbons and protons labelled with either letters or numbers*) to ease the grading of the problem set. Below are provided both examples of the solutions to be shared with the graders and the students.

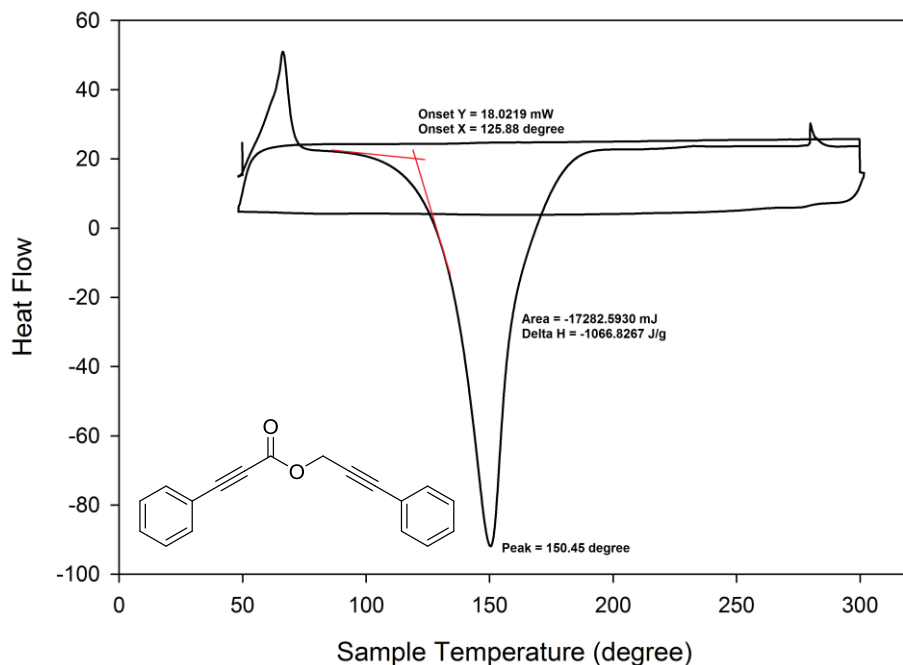
Ester 1



Ester 2



Ester 3



References:

1. Kocsis, L. S.; Brummond, K. M. Intramolecular Dehydro-Diels-Alder Reaction Affords Selective Entry to Arylnaphthalene or Aryldihydronaphthalene Lignans. *Organic Letters*, Volume: 16, Issue: 16, Pages: 4158-4161, DOI: 10.1021/ol501853y
2. U. Chinna Rajesh, Yaroslav Losovyj, Chun-Hsing Chen, and Jeffrey M. Zaleski « Designing Synergistic Nanocatalysts for Multiple Substrate Activation: Interlattice Ag-Fe₃O₄ Hybrid Materials for CO₂-Inserted Lactones » *ACS Catalysis* 2020 10 (5), 3349-3359. DOI: 10.1021/acscatal.9b04260
3. Klemm, L. H.; Gopinath, K. W.; Karaboyas, G. C.; Capp, G. L.; Lee, D. H. Syntheses and spectral studies of some dienic and enynic esters. *Tetrahedron*, 1964, 20, 871-876. DOI:10.1016/S0040-4020(01)98419-4
4. Eghbali, N.; Eddy, J.; Anastas, P. T. Silver-Catalyzed One-Pot Synthesis of Arylnaphthalene Lactones. *J. Org. Chem.* 2008, 73, 17, 6932-6935. DOI: 10.1021/jo801213m

Solutions to Case Study # 1

The Hare and the Tortoise: Slow and Steady Gets You the Correct Target!

All assignments were reached using all the spectral data available in the files provided to the students. However, few NMR peaks might still be unassigned or ambiguous and will require the use of additional more advanced spectroscopy experiments.

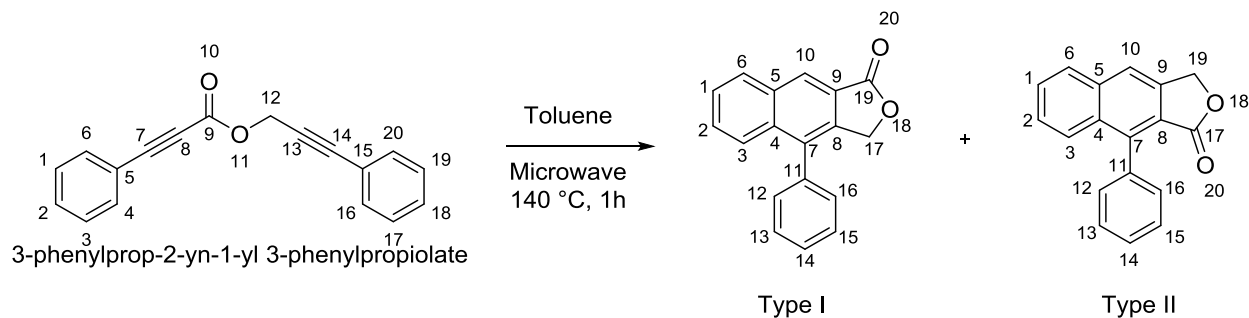


FIGURE	DESCRIPTION	PAGE
SI1	Ester 1 - ¹ H NMR	SI1
SI2	Ester 1 - ¹³ C NMR	SI2
SI3	Ester 1 - IR	SI3
SI4	Compound 1 - ¹ H NMR	SI4
SI5	Compound 1 - ¹³ C NMR	SI5
SI6	Compound 1 - APT	SI6
SI7	Compound 1 - COSY	SI7
SI8	Compound 1 - COSY (Zoom)	SI8
SI9	Compound 1 - HSQC	SI9
SI10	Compound 1 - HSQC (Zoom)	SI10
SI11	Compound 1 - HMBC	SI11
SI12	Compound 1 - HMBC (Zoom)	SI12
SI13	Compound 1 - 1D NOE	SI13
SI14	Compound 1 - IR	SI14

FIGURE	DESCRIPTION	PAGE
SI15	Compound 1 - Mass Spectra	SI15
SI16	Compound 2 - ¹ H NMR	SI16
SI17	Compound 2 - ¹³ C NMR	SI17
SI18	Compound 2 - APT	SI18
SI19	Compound 2 - COSY	SI19
SI20	Compound 2 - COSY (Zoom)	SI20
SI21	Compound 2 - HSQC	SI21
SI22	Compound 2 - HSQC (Zoom)	SI22
SI23	Compound 2 - HMBC	SI23
SI24	Compound 2 - HMBC (Zoom)	SI24
SI25	Compound 2 - HMBC (Zoom)	SI25
SI26	Compound 2 - 1D NOE	SI26
SI27	Compound 2 - IR	SI27
SI28	Compound 2 - Mass Spectra	SI28

Solutions to Case Study # 2

Can Slow, Steady and Green Get You the Correct Target?

All assignments were reached using all the spectral data available in the files provided to the students. However, few NMR peaks might still be unassigned or ambiguous and will require the use of additional more advanced spectroscopy experiments.

^1H NMR ^{13}C NMR

