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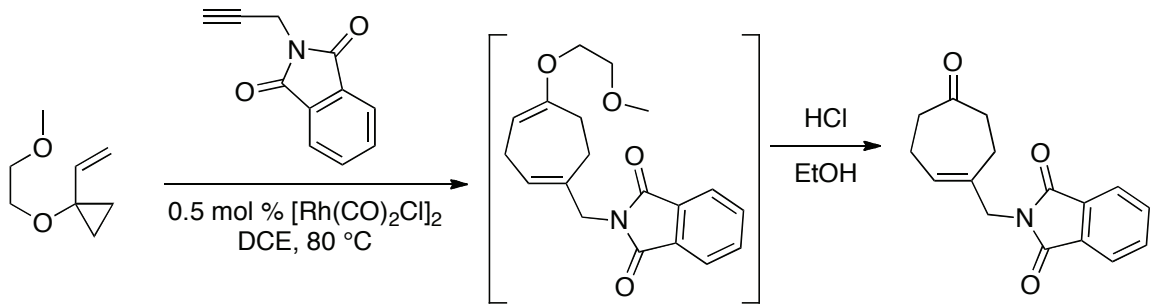
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

THE PREPARATION OF CYCLOHEPT-4-ENONES BY RHODIUM-CATALYZED INTERMOLECULAR [5+2] CYCLOADDITION



Submitted by Paul A. Wender,[1] Adam B. Lesser,[1] and Lauren E. Sirois.[1]
Checked by Kay M. Brummond and Joshua M. Osbourn.

1. Procedure[2]

2-[(5-Oxo-1-cyclohepten-1-yl)methyl]-1H-isoindole-1,3(2H)-dione. An oven-dried (>150 °C for 12 h), three-necked, 200-mL, round-bottomed flask, reflux condenser, thermometer adapter, thermometer, rubber septum, and Teflon-coated magnetic stir bar are assembled while hot, and the apparatus is cooled under a stream of nitrogen venting to a manifold (20 min). The septum is removed and the flask is charged with $[Rh(CO)_2Cl]_2$ (55.0 mg, 0.141 mmol, 0.005 equiv) (Note 1) and *N*-propargyl phthalimide (5.99 g, 32.3 mmol, 1.15 equiv) (Note 2). The rubber septum is replaced and the apparatus is gently re-flushed (5 min) with a stream of nitrogen and then kept under a positive nitrogen pressure using a mineral oil bubbler attached to the outlet. 1,2-Dichloroethane (52 mL) (Note 3) is added via syringe, and magnetic stirring is started. 1-(2-Methoxyethoxy)-1-vinylcyclopropane (VCP, 4.3 mL, 4.00 g, 28.1 mmol, 1.00 equiv) (Note 4) is added in a single portion via syringe (ca. 1 min later) (Note 5). At this time, the thermometer is immersed in the amber-colored heterogeneous reaction mixture and reads 25 °C. Under a positive pressure of nitrogen, the rubber septum is replaced by a Teflon stopper and the reaction vessel is lowered into a preheated oil bath (external bath temperature 90–100 °C). Within five min after the start of heating, the reaction mixture becomes golden yellow and homogeneous and reaches an internal reflux temperature of 82–84 °C. The progress of the reaction is followed by TLC analysis (Note 6) until consumption of the VCP is complete (25 min, during which time the homogeneous reaction solution

darkens in color from golden yellow to orange to a deep red-brown).

At this time the reaction vessel is removed from the oil bath, and stirring of the mixture is continued at ambient temperature for 90 min until the solution cools to an internal temperature of 25–30 °C. A 0.1 N HCl/EtOH solution (6.0 mL) (Note 7) is added in a single portion via syringe, and the red-brown homogeneous reaction solution is stirred at ambient temperature (30 min) until hydrolysis of the initial [5+2] cycloadduct **1** to ketone **2** is complete (as determined by TLC analysis) (Note 6). The solution is then transferred to a 1-L, round-bottomed flask. Two portions (75 mL each) of diethyl ether are used to rinse the reaction vessel and are combined with the transferred reaction solution (Note 8). Silica gel (30 g) (Note 9) is added, and the resulting slurry is concentrated in vacuo by rotary evaporation (Note 10) until the apricot-colored dry silica flows freely in the flask (Note 11).

The dry silica is loaded onto a chromatography column (pre-packed with a slurry of 260 g of silica gel in a 40% ethyl acetate/hexanes mixture), and the product is eluted using the same solvent mixture (Note 12). Collection of 25 mL fractions begins immediately, and product-containing fractions (as determined by TLC analysis) (Note 6) are combined in a 1-L round-bottomed flask and concentrated in vacuo using a rotary evaporator (37 °C bath, 10 mm Hg) to give a viscous, pale yellow oil. This oil is then transferred to a 500-mL, round-bottomed flask using successive rinses of dichloromethane (100 mL total volume). Evaporation of solvent (rotary evaporator followed by 12 h under high vacuum) (Notes 10 and 13) provides the purified [5+2] cycloadduct **2** as an off-white, powdery solid, mp = 71–73 °C (6.84 g, 90% yield) (Notes 14 and 15). The submitters report 95-96% yield (7.2-7.3 g) of **2** (mp = 71-72 °C) using freshly prepared 1-(2-methoxyethoxy)-1-vinylcyclopropane.

2. Notes

1. Chlorodicarbonylrhodium(I) dimer was purchased in 500 mg batches from Strem Chemicals, Inc. (product 45-0450), and stored at –20 °C in a vacuum sealed desiccator. The deep red crystalline complex was used as received.

2. *N*-Propargyl phthalimide (97%) was purchased from Sigma-Aldrich (product 696072) and used as received (white crystalline solid).

3. 1,2-Dichloroethane (99.8%) was purchased from Sigma-Aldrich

(product 34872) and distilled over calcium hydride under a nitrogen atmosphere prior to use.

4. 1-(2-Methoxyethoxy)-1-vinylcyclopropane was purchased in 1-gram ampules from Sigma-Aldrich (product 666246). For larger-scale applications, it can be prepared according to reference 2. Storage at –20 °C is recommended (colorless liquid).

5. For [5+2] reactions in general: when the alkyne is a liquid at ambient temperature, it is often preferable to add it to the reaction mixture last, in a single portion via syringe immediately after addition of the VCP. While not pertinent to the specific reaction conditions described above, when $[Rh(CO)_2Cl]_2$ is to be used for an intermolecular [5+2] cycloaddition at a higher catalyst loading (e.g., 5 mol %), it is advisable to purge the solution containing the catalyst and VCP (via bubbling of nitrogen from an immersed needle for ca. 10 min) prior to addition of the alkyne. This minimizes background rhodium-catalyzed formation of [5+2+1] cycloadducts[24] from any carbon monoxide liberated upon interaction of the VCP with $[Rh(CO)_2Cl]_2$ (the presumed liberation of CO gas is sometimes noticeable in the form of gentle bubbling).

6. Thin-layer chromatography analysis was performed on glass-backed, silica-coated plates purchased from EMD Chemicals, Inc. (silica gel 60 F_{254}, product 5715-7). Plates were eluted with a 50% EtOAc/hexanes mixture and visualized using short wave ultraviolet light (254 nm) and *p*-anisaldehyde stain (followed by gentle heating). 1-(2-Methoxyethoxy)-1-vinylcyclopropane has a R_f = 0.64 (purple), *N*-propargyl phthalimide has a R_f = 0.53 (UV-active), the [5+2] enol-ether intermediate **1** has a R_f = 0.45 (UV-active, blue), and the [5+2] ketone product **2** has R_f = 0.36 (UV-active, blue).

7. A 0.1 N hydrochloric acid solution was prepared by dilution of 12.1 N "concentrated" HCl (Fisher Scientific) with a pre-mixed solution of ethanol (95%, 190 proof, Fisher Scientific) and distilled water (98:2, EtOH:H_2O, vol:vol).

8. Unless otherwise noted, all solvents were purchased from Fisher Scientific and used as received.

9. Silica gel (40-63 μm, 60 Å) was purchased from Sorbent Technologies (product 30930M-25) and used as received.

10. The vacuum for the rotary evaporator was established using a water aspirator (ca. 10 mmHg). The water bath was slowly heated from 25 to 45 °C.

11. If desired for other [5+2] reactions, as an alternative to adsorption of the crude product on silica gel, a concentrated solution can be loaded onto the packed column for flash chromatography conducted as described in reference 3. When direct adsorption is not performed, it is preferable to filter the post-quench reaction solution through a short pad of silica gel (eluting with Et_2O or EtOAc) in order to prevent decomposition of potentially acid-sensitive products upon concentration for column loading.

12. The column is 70 mm wide and the height of the silica is 7 inches inside the column. After the silica containing the adsorbed crude product is poured over the pre-packed column bed, the 1-L vessel is rinsed with enough eluent to gently cover the additional silica. Sand and more eluent are added and forced-flow flash chromatography proceeds normally. The [5+2] product **2** is detected in fractions 56-82.

13. High vacuum is measured at <0.1 mm Hg via a digital manometer. The submitters state that if product **2** does not solidify upon initial exposure to high vacuum (up to 10 min), the viscous oil can be suspended in pentane (100 mL) and the flask immersed in a sonication bath for 5 min, followed by repeated rotary evaporation and static high vacuum to remove any trapped higher-boiling solvents.

14. Analytical data for product **2**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.39–2.34 (m, 4 H), 2.65–2.59 (m, 4 H), 4.23 (s, 2 H), 5.81 (t, J = 5.5 Hz, 1 H), 7.77–7.73 (m, 2 H), 7.88–7.85 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 23.3, 25.8, 41.5, 42.0, 44.7, 123.3, 126.7, 131.8, 134.0, 135.1, 168.0, 212.6; IR (film, NaCl plate): 3467, 2915, 2848, 1770, 1708, 1612 cm^{-1}; MS (ESI+) *m*/*z* (relative intensity): 287 ($[M+NH_4]^+$, 100%), 270 ($[M+H]^+$, 58%); Exact mass (ESI+) $[M+H]^+$ calcd. for $C_{16}H_{16}NO_3$: 270.1130. Found: 270.1118; Anal. calcd. for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.24; H, 5.67; N, 5.16.

15. The submitters report >99% purity by gas chromatography: Agilent 7890A GC / 5975C inert MSD. Column: Agilent HP-5MS (part no: 19091S-433I), length: 30 m, I.D.: 0.25 mm, film: 0.25 μm, injector temperature: 280 °C, split ratio: 1/100. Temperature program: 35 °C for 3.75 min → 320 °C, 20 °C/min, then 320 °C for 7 min. The product **2** has a retention time of 16.65 min (injected as a solution in EtOAc).

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

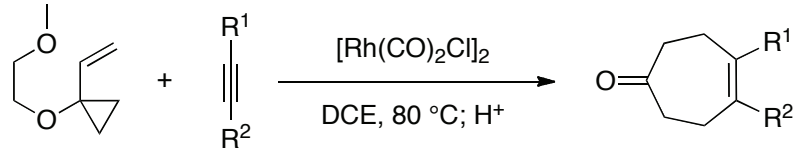
The design and discovery of new reactions are of singular importance in efforts to synthesize molecules in a step economical and green, if not ideal, fashion.[4] New reactions provide new ways to think about bond construction, thereby creating new strategies and process options. While cycloadditions, such as the Diels-Alder [4+2] reaction,[5] have historically played a major role in organic synthesis, the introduction of new cycloadditions for medium-sized ring synthesis has only recently received attention. Metal-mediated and metal-catalyzed cycloadditions have figured prominently in such efforts.[6] The metal-catalyzed [5+2] cycloaddition of vinylcyclopropanes (VCPs) and π-systems was first introduced in 1995. It is a homolog of the Diels-Alder [4+2] reaction, in which a 5-carbon, 4-electron VCP conceptually replaces a 4-carbon, 4-electron diene.[7] Since the initial report involving tethered VCPs and alkynes,[7] the rhodium(I)-catalyzed intramolecular process has proven effective with other two-carbon π-components, such as alkenes[8] and allenes.[9] The rhodium-catalyzed intermolecular process has likewise been reported between VCPs and alkynes[10] or allenes.[11] While 1-(2-methoxyethoxy)-1-vinylcyclopropane is a convenient cycloaddition partner due to its synthetic accessibility and commercial availability, the intermolecular [5+2] reaction can also be conducted readily with 1-siloxy-VCPs or 1-alkyl-VCPs.[10]

Further development of the intramolecular [5+2] cycloaddition has included the introduction of new catalysts, some featuring alternative metals (namely, Ru, Fe, and Ni, although Rh remains the most effective metal for many cases).[12] Ligands have also been varied. A water-soluble catalyst has been introduced for conducting the cycloaddition in water or aqueous mixtures.[13] Chiral catalysts have also been reported that provide, in many cases, excellent enantioselectivity.[14] The [5+2] reaction has been reported to occur in the temperature range of –23 to 110 °C (depending on the substrates and catalyst employed); some of the most active catalysts effect the [5+2] reactions of VCPs and alkynes in minutes at room temperature and in high

yields.[15] The functional group tolerance of the metal-catalyzed [5+2] cycloaddition is generally excellent, as evident from the representative substrate scope detailed in Table 1 (for 1-(2-methoxyethoxy)-1-vinylcyclopropane and various alkynes, $[Rh(CO)_2Cl]_2$ as the catalyst).[2] Rhodium-catalyzed [5+2] cycloadditions are generally most effective in dichloromethane (DCM), 1,2-dichloroethane (DCE), and 2,2,2-trifluoroethanol (TFE). However, the reaction can also be conducted in non-halogenated solvents, such as ethers (tetrahydrofuran and 2-methyl-THF, for example), acetone, and toluene, depending on the catalyst. Reaction concentrations of up to 0.5-1.0 M have been reported, with no or minimal loss in product yield in many cases.

The mechanism of the rhodium-catalyzed process has been investigated computationally, providing a theoretical foundation for understanding differences in rate for various VCPs and π-components.[16] The regioselectivity of both intra- and intermolecular [5+2] reactions has also been explored, along with some aspects of diastereoselectivity.[17] Partly as a result of the studies and improvements referenced herein, the [5+2] reaction has found increasing use in organic synthesis[18] as well as in the generation of small-molecule libraries.[19] The development of serial/tandem/ cascade/domino transformations is one focus of ongoing efforts to achieve step economy in synthesis.[20] Examples of cascade catalysis or serialized processes based on the [5+2] reaction include single-flask [5+2]/Nazarov cyclizations, tandem [5+2]/[4+2] cycloadditions, and tandem allylic substitutions/[5+2] cycloadditions.[21] Significantly, the metal-catalyzed [5+2] reaction has also provided inspiration for the introduction of other new reactions, such as the [6+2] cycloaddition of vinylcyclobutanones and π-systems,[22] the [5+2] cycloaddition of allenylcyclopropanes and π-systems,[23] and higher-order, multicomponent cycloadditions, such as [5+2+1] and [5+2+1+1] reactions.[24]

Table 1.[2] Representative Intermolecular [5+2] Cycloadditions of 1-(2-Methoxyethoxy)-1-vinylcyclopropane and Alkynes using $[Rh(CO)_2Cl]_2$[a]



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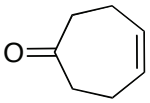
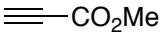
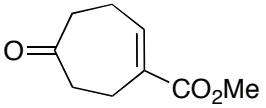
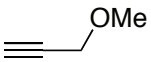
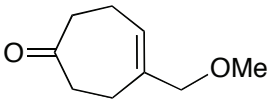
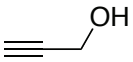
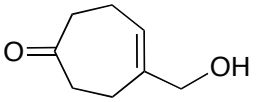
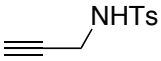
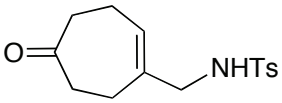
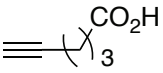
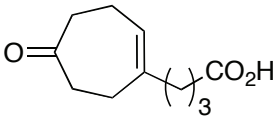
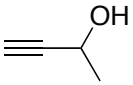
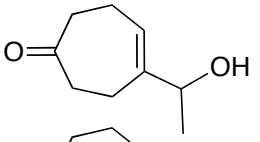
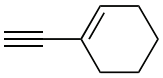
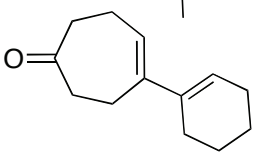
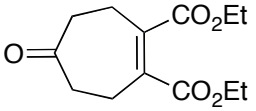
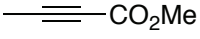
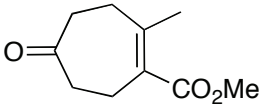
1		2 h	75%	
2		10 min	84%	
3		15 min	92%	
4		25 min	82%	
5		15 min	87%	
6		1.5 h	87%	
7		12 min	89%	
8		7 h[c]	85%	
9		1 h	96%	
10		2 h	81%	

[a] Reaction conditions: 1-(2-methoxyethoxy)-1-vinylcyclopropane (1 mmol), alkyne (1.2-1.3 mmol), $[Rh(CO)_2Cl]_2$ (0.005 mmol), DCE (0.5 M concentration with respect to VCP), 80 °C; 1% HCl/MeOH, room temp. [b] Isolated yield of purified product. [c] Reaction conducted at room temp.

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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

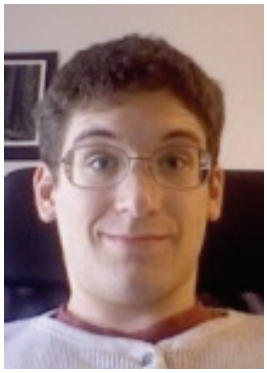
Chlorodicarbonylrhodium dimer: Di-μ-chloro-bis(dicarbonylrhodium): Tetracarbonyldi-μ-chlorodirhodium; (14523-22-9)

N-Propargylphthalimide: Phthalimide, *N*-2-propynyl-: 1*H*-Isoindole-1,3(2*H*)-dione, 2-(2-propynyl)-; (7223-50-9)

1,2-Dichloroethane: 1,2-Ethylene dichloride; (107-06-2)

1-(2-Methoxyethoxy)-1-vinylcyclopropane: Cyclopropane, 1-ethenyl-1-(2-methoxyethoxy)-; (278603-80-8)

Paul A. Wender was born in Pennsylvania. He completed his B.S. degree in Chemistry at Wilkes College in 1969 and his Ph.D. at Yale University in 1973 with Prof. Frederick E. Ziegler. After pursuing postdoctoral studies with Prof. Gilbert Stork at Columbia University as an NIH Fellow, he joined the faculty at Harvard University in 1974 and subsequently moved to Stanford University where he is currently the Bergstrom Professor of Chemistry and Professor (by courtesy) of Chemical and Systems Biology.

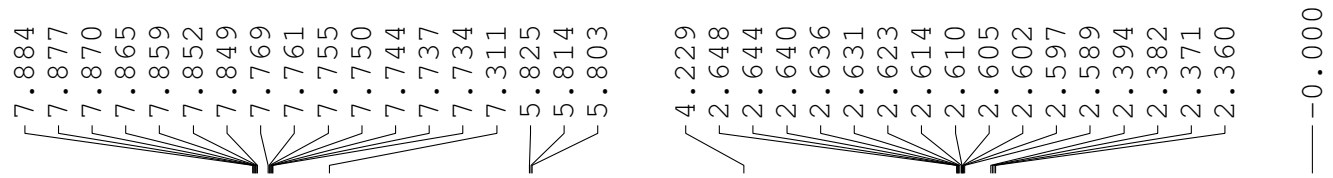


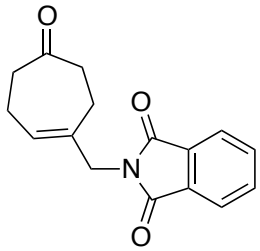
Adam Lesser was born in Massachusetts in 1983. He received his B.S. with honors in Chemistry from Trinity College (Hartford, CT) in 2006, where he performed undergraduate research on metallacyclic peptides in the lab of Prof. Timothy P. Curran. A recipient of Amgen and Eli Lilly graduate fellowships, Adam is currently a Ph.D. student in Prof. Wender's lab at Stanford University.

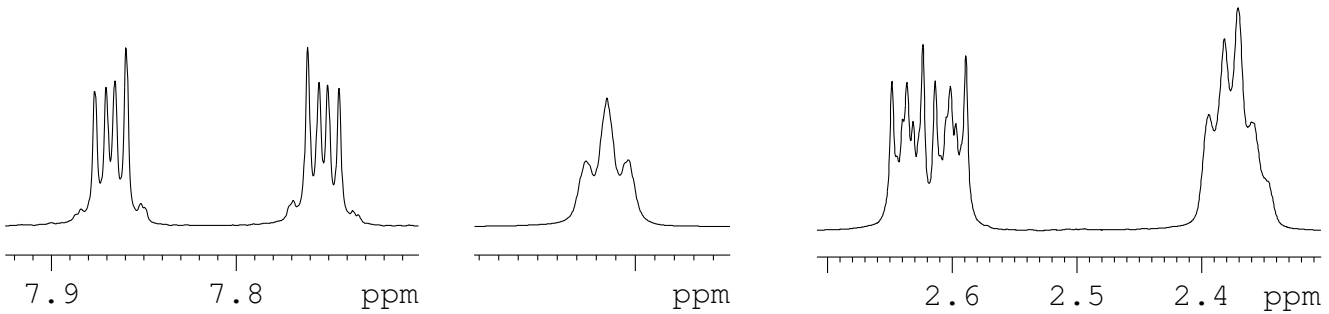
Lauren Sirois is a native of Massachusetts and New Hampshire. She obtained her A.B. in Chemistry in 2004 from Harvard College, where she conducted undergraduate research in C-H functionalization methods under the direction of Prof. M. Christina White. A recent National Science Foundation Fellow, Lauren is currently completing her Ph.D. studies in Prof. Wender's group at Stanford University.

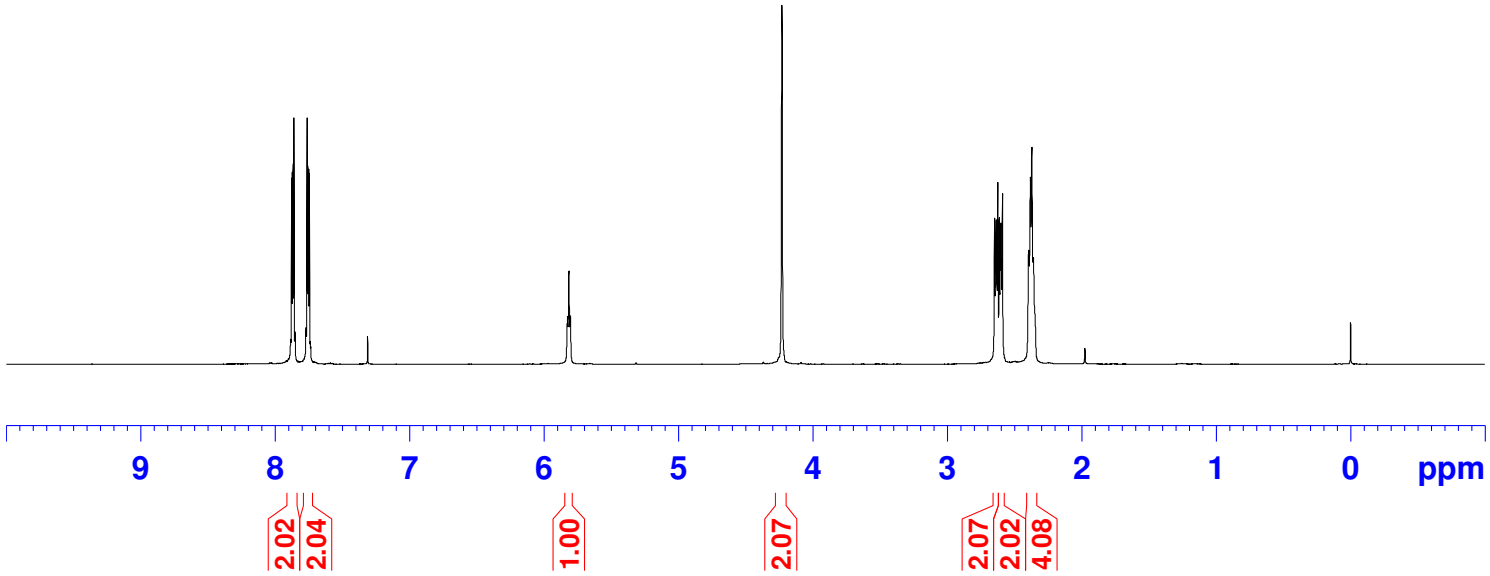
Joshua Osbourn received his B.S. degree in chemistry from West Virginia University in 2007. He then joined the graduate program at the University of Pittsburgh and is working towards a Ph.D. under the direction of Professor Kay M. Brummond. His current research involves the thermal [2 + 2] cycloaddition reactions of allene-ynes.

CDCl3 + TMS, 500MHz







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PROCNO                       1

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PULPROG                  zg30
TD                      65536
SOLVENT                 CDCl3
NS                           8
DS                           2
SWH                10330.578 Hz
FIDRES              0.157632 Hz
AQ                 3.1719923 sec
RG                          32
DW                    48.400 usec
DE                     6.50 usec
TE                     293.7 K
D1                2.00000000 sec

======== CHANNEL f1 ========
NUC1                        1H
P1                      10.20 usec
PLW1            18.74300003 W
SFO1            500.1630887 MHz

F2 - Processing parameters
SI                      65536
SF              500.1599854 MHz
WDW                        EM
SSB          0
LB                      0.30 Hz
GB           0
PC                      1.00
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