Published in final edited form as:

Org Lett. 2011 April 1; 13(7): 1781–1783. doi:10.1021/ol200244p.

Microwave Assisted Synthesis of Bridgehead Alkenes

Leah Cleary, Hoseong Yoo, and Kenneth J. Shea*

Department of Chemistry, University of California, Irvine, 1102 Natural Sciences 2, Irvine, California, 92697-2025

Abstract

A new, concise method to synthesize triene precursors for the type 2 intramolecular Diels–Alder reaction has been developed. Microwave irradiation of the trienes provides a convenient method for the synthesis of bridgehead alkenes. Higher yields, shorter reaction times and lower reaction temperatures provide a general and efficient route to this interesting class of molecules.

The type 2 intramolecular Diels–Alder (IMDA) reaction is a powerful tool for the construction of polycyclic compounds containing bridgehead alkenes.ⁱ Highly strained bicyclo[*n*.3.1], ii–11 five–seven fused,¹² azobicyclo[*n*.3.1],^{liii} and caprolactam ring systems^{liv} can all be synthesized with high regio- and stereo-selectivity utilizing this reaction. Application as a key carbon–carbon bond forming step in the syntheses of complex molecules aptly displays the synthetic significance of the reaction.^{lv,16}

The type 2 IMDA reaction has an elevated activation free energy as compared to the type 1 IMDA variant due in part to the formation of a strained bridgehead alkene and the cumulative non-bonding interactions that develop in the transition state leading to the bridged bicyclic product. Experimental values of the activation free energy ($\Delta G^\ddagger$) for the reaction range from approximately 37–41 kcal/mol (210 °C).⁸ This energy barrier is overcome with either elevated reaction temperatures for extended periods of time^{3,4} or by the use of Lewis acid catalysis.⁶ In a complex molecule setting, Lewis acid activation is often prohibited due to the presence of more sensitive functional groups.¹⁶ Solution phase thermolysis is then necessary to induce cycloaddition of highly functionalized trienes, however, this often requires temperatures in excess of 200 °C with reaction times of several hours. The yields of these reactions are often compromised by competing decomposition of the diene under these harsh and prolonged conditions. Alternately, use of microwave radiation has been known to decrease reaction times and lower temperatures for reactions carried out under thermal conditions.^{17,18} A microwave reactor also provides a more convenient, safer method for heating reactions to the temperatures necessary for the type 2 IMDA reaction to occur. We thus set out to develop a straightforward method using

kjshea@uci.edu .

Supporting Information Available Experimental procedures, spectroscopic data (¹H NMR, ¹³C NMR, IR, HR-MS) for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

microwave irradiation to accomplish the cycloadditions with Diels–Alder reaction precursors that incorporate a range of substitution patterns.

A succinct method to synthesize these triene substrates was designed (Scheme 1). Utilizing enyne metathesis, alkynes can be viewed as protected dienes. Under 300 psi of ethylene, iodoalkyne **1**¹⁹ was converted to diene **2**. Iododiene **2** was then coupled with acid chloride **3** or **4** to furnish trienes **5** or **6**, respectively. Similarly diester **13** can be synthesized from pentynol **7** (Scheme 2). Silyl protection of the alcohol followed by alkyne metathesis gave diene **9**. After deprotection of the silyl group and condensation of the resulting alcohol with acid chloride **4**,²⁰ triene **13** was obtained. Triene **14** was synthesized analogously starting from pentynol **8**.

Triene **5** was chosen as a standard substrate for optimization of the microwave conditions (Table 2). Cinnamyl derived dienophiles are poor performers and this would allow us to more effectively optimize the reaction. Because of the high temperatures necessary to induce cycloaddition when thermal conditions are employed, we chose aromatic solvents with high boiling points for the reactions. We initially found that heating in toluene was ineffective for conversion to the cycloadduct, likely due to starting material decomposition during the ramp time for the reaction to reach 200 °C. Switching solvents to *o*-dichlorobenzene and heating to 220 °C resulted in a modest yield of 47%. By incrementally decreasing the temperature we found that a temperature of 160 °C product yield increased to 73%. We were surprised to find that the reaction proceeded at temperatures as low as 140 °C, however, this required longer reaction times and the yield was reduced to 65%. The addition of base to buffer any adventitious acid did not improve the yield. Lastly, for direct comparison of the optimized microwave conditions to thermal conditions we heated triene **5** in a sealed tube. No cycloaddition occurred under thermal conditions at 160 °C after 10 hours. Full conversion of the starting material occurred only after heating to 240 °C for 4 hours, providing a modest 45% yield.

Conditions for substrates in which a carbonyl group is not part of the diene–dienophile tether differ from the cinnamyl derived substrate (Table 2). Triene **16** decomposed under microwave irradiation in *o*-dichlorobenzene. As was found when optimizing the cycloaddition of triene **5**, the use of *o*-xylene as the solvent also lead to extensive decomposition of the starting material. We hoped to exploit the fact that the addition of ions or polar solvent facilitates the rapid heating of a nonpolar solvent.^{7b} When the reaction was run in *o*-xylene “doped” with DMSO, the ramp time to 200 °C was reduced to under four minutes and a 75% yield of cycloadduct **21** was obtained. Triene **17** under thermal conditions requires heating to 240 °C for 4 hours to obtain a 64% yield. Again, the triene decomposed in *o*-dichlorobenzene but using *o*-xylene and DMSO as solvent for the microwave assisted reaction gave cycloadduct **17** in 75% yield in an abbreviated 6 hour reaction time.

A series of trienes were subjected to optimized microwave conditions. These specific trienes were chosen because thermal conditions resulted in yields ranging from 40–60%.⁴ Under microwave conditions, triene **14** underwent cycloaddition to provide a 90% yield of cycloadduct **22** in toluene under microwave conditions. The cycloadditions of diesters **6** and **13** were also performed in toluene and resulted in 89% and 92% yields, respectively. The ramp time for the toluene reactions is approximately 25 minutes, however, the yields are excellent as compared to the cycloaddition of trienes **16**⁵ and **17**³ in *o*-xylene. This discrepancy may be attributed to trienes **6–14** possessing a less polarized dienophile reducing any nucleophilic attack or polymerization. We also note that under these conditions, yields are independent of steric constraints that arise from shortening the tether length from 6 to 4 atoms. Furthermore, the cycloaddition of triene **14** with a tether length of

six atoms does not yield any of the [6.2.2] cycloadduct, the regioisomer that is formed under Lewis acid catalyzed conditions.

The more concise synthesis of requisite trienes rapidly affords substrates for the type 2 IMDA reaction. Microwave reactors provide optimal conditions for the subsequent cycloaddition to afford bridgehead alkenes. We found that all substrates require less reaction time and lower temperatures to provide cycloadducts in higher yields. In many cases, the cycloaddition reaction times are similar to catalyzed reactions without the necessity of stoichiometric quantities of Lewis acid. Microwave conditions are also safer than traditional thermolysis because the reactor is built to handle the increased pressures caused by high temperatures necessary cycloaddition to occur. Finally, regioselectivity to form the 1,3-regioisomer was conserved even for longer tether lengths.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Authors would like to thank Dr. John Greaves (UC Irvine) for assistance with GC-MS analysis and Drs. Katy Bridgwood and Grant Shibuya (UC Irvine) for helpful advice. This research was supported in part by the National Institutes of Health.

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Scheme 1.
Expediant triene synthesis

Scheme 2.
Synthesis of trienes with diester dienophiles

Table 1

Optimization of the type 2 IMDA reaction conditions.

entry	solvent	temperature	time	base	yield
1	toluene	160 °C	1 h	-	0%
2	<i>o</i> -DCB	220 °C	1 h	-	47%
3	<i>o</i> -DCB	180 °C	1 h	-	66%
4	<i>o</i> -DCB	160 °C	1 h	-	73%
5	<i>o</i> -DCB	140 °C	1.5 h	-	65%
6	<i>o</i> -DCB	140 °C	1 h	-	^a
7	<i>o</i> -DCB	160 °C	1 h	DTBP	^b
8 ^c	<i>o</i> -DCB	160 °C	10 h	-	0%
9 ^c	<i>o</i> -DCB	240 °C	4 h	-	45%

^a Reaction was incomplete and product could not be separated from starting material.

^b An inseparable mixture of products was formed.

^c Conventional heating was employed.

Table 2

Alternate conditions of the type 2 IMDA.

entry	conditions	product	yield
16	DCB, 200 °C, 6 h, μ W	18	0%
	<i>o</i> -xylenes, 200 °C, 6 h, μ W		0%
	<i>o</i> -xylenes, 0.1 equiv DMSO, 200 °C, 6 h, μ W		75%
	<i>o</i> -xylenes, 240 °C, 15 h		64%
17	DCB, 220 °C, 6 h, μ W	19	0%
	<i>o</i> -xylenes, 0.1 equiv DMSO, 200 °C, 6 h, μ W		75%
6	toluene, 160 °C, 1 h, μ W	20	92%
13	toluene, 160 °C, 1 h, μ W	21	89%

entry	conditions	product	yield
14	toluene, 160 °C, 1 h, μ W	22	90%