

# Microwave Assisted Synthesis of Bridgehead Alkenes

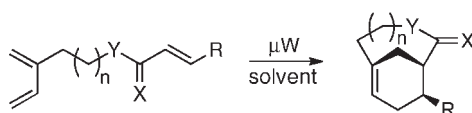
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Received January 25, 2011

## 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.<sup>1</sup> Highly strained bicyclo[*n*.3.1],<sup>2–11</sup> five–seven fused,<sup>12</sup> azobicyclo[*n*.3.1],<sup>13</sup> and caprolactam ring systems<sup>14</sup> can all be synthesized with high regio- and stereoselectivity 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.<sup>15,16</sup>

Compared to the type 1 IMDA variant, the type 2 IMDA reaction has an elevated activation free energy. This difference is due to the formation of a strained bridgehead alkene and the cumulative nonbonding 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 to 41 kcal/mol (210 °C).<sup>8</sup> This energy barrier is overcome with either elevated reaction temperatures for extended periods of time<sup>3,4</sup> or by the use of Lewis acid catalysis.<sup>6</sup> In a complex molecule setting, Lewis acid activation is often prohibited due to the presence of more sensitive functional groups.<sup>16</sup> Solution phase thermolysis is then necessary to induce cycloaddition of highly functionalized trienes; however, this often requires temperatures

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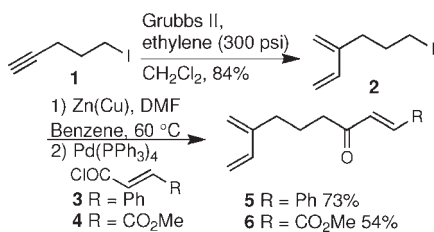
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in excess of 200 °C with reaction times of several hours. The yields of these reactions are often compromised by competing decomposition of the diene under these harsh and

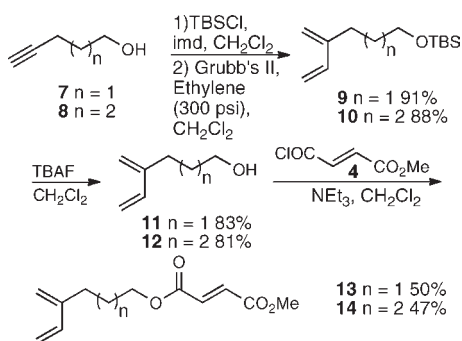
### Scheme 1. Expedient Triene Synthesis



prolonged conditions. Alternately, use of microwave radiation has been known to decrease reaction times and lower temperatures for reactions carried out under thermal conditions.<sup>17,18</sup> 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 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**<sup>19</sup> 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**,<sup>20</sup> triene **13** was obtained. Triene **14** was synthesized analogously starting from pentynol **8**.

### Scheme 2. Synthesis of Trienes with Diester Dienophiles



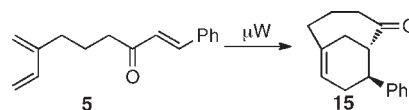
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Triene **5** was chosen as a standard substrate for optimization of the microwave conditions (Table 1). Cinnamyl-

**Table 1.** Optimization of the Type 2 IMDA Reaction Conditions



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

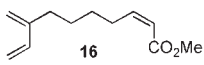
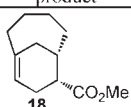
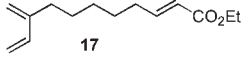
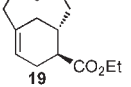
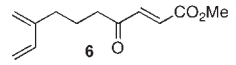
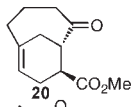
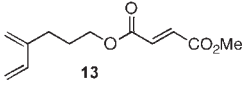
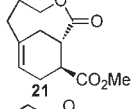
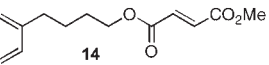
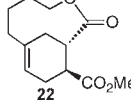
<sup>a</sup> Reaction was incomplete, and product could not be separated from starting material. <sup>b</sup> An inseparable mixture of products was formed. <sup>c</sup> Conventional heating was employed.

derived dienophiles are less reactive substrates for the Diels–Alder reaction and thus provide a more useful platform for optimization of the reaction conditions. 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 at a temperature of 160 °C the 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 h. Full conversion of the starting material occurred only after heating to 240 °C for 4 h, 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

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**Table 2.** Alternate Conditions of the Type 2 IMDA

entry	conditions	product	yield
 <b>16</b>	DCB, 200 °C, 6 h, $\mu$ W	 <b>18</b>	0%
	<i>o</i> -xylenes, 200 °C, 6 h, $\mu$ W		0%
	<i>o</i> -xylenes, 0.1 equiv DMSO, 200 °C, 6 h, $\mu$ W		75%
 <b>17</b>	<i>o</i> -xylenes, 240 °C, 15 h	 <b>19</b>	64%
	DCB, 220 °C, 6 h, $\mu$ W <i>o</i> -xylenes, 0.1 equiv DMSO, 200 °C, 6 h, $\mu$ W		0% 75%
 <b>6</b>	toluene, 160 °C, 1 h, $\mu$ W	 <b>20</b>	92%
 <b>13</b>	toluene, 160 °C, 1 h, $\mu$ W	 <b>21</b>	89%
 <b>14</b>	toluene, 160 °C, 1 h, $\mu$ W	 <b>22</b>	90%

**5**, the use of *o*-xylene as the solvent also lead to extensive decomposition of the starting material. It was hypothesized that the extended ramp time necessary to heat the nonpolar solvents permitted the gradual 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.<sup>18</sup> When the reaction was run in *o*-xylene “doped” with DMSO, the ramp time to 200 °C was reduced to under 4 min and a 75% yield of cycloadduct **21** was obtained. Under thermal conditions, triene **17** requires heating to 240 °C for 4 h 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 h 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 to 60%.<sup>4</sup> 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 min; however, the yields are excellent as compared to the cycloaddition of trienes **16**<sup>5</sup> and **17**<sup>3</sup> 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 those of 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 for cycloaddition to occur. Finally, regioselectivity to form the 1,3-regioisomer was conserved even for longer tether lengths.

**Acknowledgment.** The 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.

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