

[ E0015 ]



## Temperature and Time Optimization of Diels-Alder Reactions in the CEM Microwave

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### Abstract:

Microwave organic chemistry is a novel technique which allows for the rapid high yield synthesis of products. As conventional syntheses are converted into microwave reactions, optimizations of these processes can help identify baseline parameters that are common in all microwave environments. Specifically, the optimizations of the Diels-Alder reactions, a common reaction in organic chemistry, were found to range between 5 and 10 minutes and 125 °C to 150 °C in the CEM microwave. This can be used as a baseline when an unknown Diels-Alder reaction is attempted.

### Introduction:

Microwave organic chemistry has expanded exponentially over the last twenty years, due to its easy setup, rapid turn around, and high yields.<sup>1,2</sup> There are many advantages of microwave chemistry over conventional synthesis. Microwave chemistry occurs through the rapid absorption of energy into molecules which contain dielectric constants, enabling faster transitions into desired products.<sup>3</sup> The rapid reaction time of microwave chemistry, often within minutes, permits increase product yields and decreased energy requirements while producing enantiomerically pure products.<sup>4</sup>

Often the transition of conventional reactions into the microwave environment needs to be optimized for peak product yield. Optimization of microwave reactions can often set a baseline for initial reactions to be done even when product yields are unknown. Microwave reactions are optimized through the manipulation of time (often within minutes) and temperature with the pressure being allowed to vary.

One important reaction that has been that has transitioned into the microwave environment is that of the Diels-Alder reaction. Diels-Alder reactions are some of the most used reactions in organic chemistry due to their easy setups and high yields. Although several papers have utilized the Diels-Alder reaction under microwave conditions, no paper has optimized the reaction in a monomode microwave. We sought

to optimize several Diels-Alder reactions in a CEM monomode microwave to determine a systemic series of parameters to use for unknown reactions.

### Experimental:

Eight reactions were chosen to determine the highest yields. Times ranged between 5 and 20 minutes while temperatures were varied from 125 °C to 175°C. All parameters are shown in the supplementary section. Temperatures were not increased over 175°C due to fear of reactant breakdown. A CEM Discover microwave was used. Times were not increased over 20 minutes due to the possibility of a retro Diels-Alder reaction. All reagents were purchased from Sigma-Aldrich and were used without further purification. Percent yields were determined by a Varian CP 3380 and a Saturn 2000. Some the products were identified by a Bruker 400 MHz and rebuilt 90 MHz NMR Anasazi Instrument.

Table 1. Reaction table containing reactants and amounts

### Reaction Table

Reaction	Reactant 1		Reactant 2	
1	Maleic Anhydride	0.20 g	1,3-Cyclohexadiene	0.16 g
2	Maleic Anhydride	0.20 g	$\alpha$ -Terpinene	0.14 g
3	Maleic Anhydride	0.20 g	$\alpha$ -Phellandrene	0.14 g
4	N-Methyl Maleimide	0.20 g	1,3-Cyclohexadiene	0.28 g
5	N-Methyl Maleimide	0.20 g	$\alpha$ -Terpinene	0.16 g
6	N-Methyl Maleimide	0.20 g	$\alpha$ -Phellandrene	0.16 g
7	Maleic Anhydride	0.20 g	Furfuryl Amine	0.20 g
8	N-Methyl Maleimide	0.20 g	Furfuryl Amine	0.23 g

### Results:

The percent yields are the results of the Diels-Alder synthesis in the CEM microwave.

Table 2. Percent Yields of the Diels Alder Reactions

### Percent Yield

Reaction	A	B	C	D	E	F	G	H	I
1	90.66	90.09	95.60	87.14	89.52	x	x	x	x
2	64.41	70.20	66.80	64.83	73.34	77.41	74.95	79.38	75.94
3	30.05	65.93	40.97	0.00	6.05	x	x	x	x
4	75.09	97.63	82.36	72.24	62.99	x	x	x	x
5	88.00	90.89	84.18	86.88	74.69	74.11	x	x	x
6	64.40	62.28	57.25	57.59	58.76	44.52	x	x	x
7	67.70	78.53	75.36	61.66	42.71	x	x	x	x
8	78.13	86.25	90.71			x	x	x	x

Conditions listed in Supplemental Material.



The molecules below are the products found from the microwave reactions.

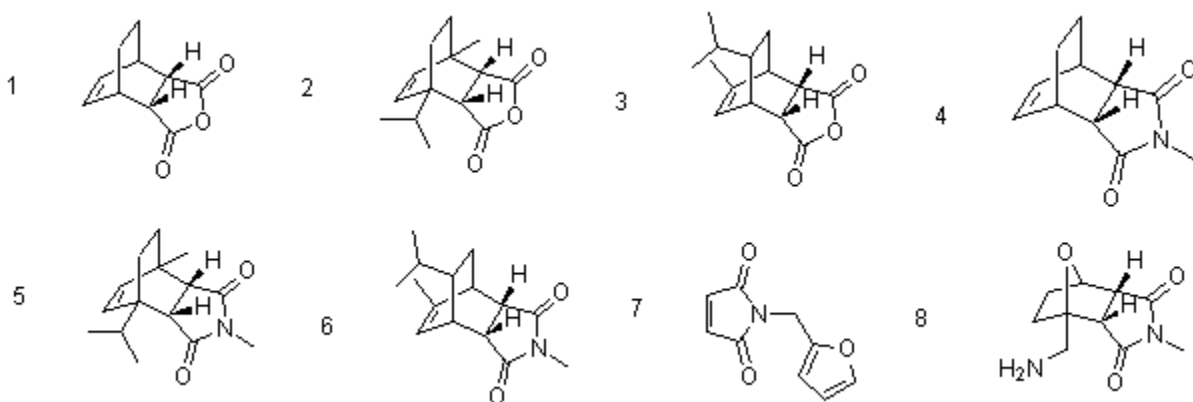


Figure 1. Structures of Products

### Discussion:

Molecules 2, 3, 4, and 7 were found that 10 minutes at 125°C showed the maximum percent yield. Molecule 7 is not shown as the Diels-Alder product <sup>de</sup>p<sup>t</sup>C and <sup>13</sup>C NMR indicated that the cyclic imide was the major product. Specifically the placement of the tetrahedral carbon at ~ 150 indicates that the imide is the primary product. The rest of the molecules were centered around 5 minutes – 10 minutes at approximately 150 °C. Only molecule 2 needed 20 minutes at 150 °C to obtain maximum percent yield.

Table 3. Optimal Parameters of the Diels Alder Reactions in the CEM Microwave

Optimization of Synthesis Results		
Reaction	Time (minutes)	Temperature (°C)
1	5	150
2	20	150
3	10	125
4	10	125
5	10	125
6	5	125
7	10	125
8	5	150

### Conclusion:

Overall many of the Diels-Alder reactions were able to react with times between 5 to 10 minutes and temperature between 125 °C to 150 °C.

**endo-Bicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic anhydride (1):** 1,3-Cyclohexadiene (0.10 g, 1.24 mmol) and maleic anhydride (0.12 g, 1.24 mmol) were thoroughly mixed in a CEM vial with a stirrer. This was capped and heated in a CEM Discover microwave for 5 min at 150 °C. This was rapidly cooled to rt yielding a white solid. The material was purified with a silica column (10 g) using EtOAc : Acetone (1:1) affording a white solid (0.14 g, 63%), mp 140–142 °C. [144–147 °C<sub>23</sub>]; <sup>1</sup>H-NMR (400 MHz) in CDCl<sub>3</sub> : δ (ppm) = 6.30 (dd, J = 3.0, 4.5 Hz, 2H), 3.17 (m, 2H), 1.61 (m, 4H), 1.39 (bd, J = 7.5 Hz, 4H), <sup>13</sup>C-NMR (100 MHz) in CDCl<sub>3</sub>: δ (ppm) = 173.89 (C=O), 132.82 (CH), 44.53 (CH), 31.42 (CH), 22.69 (CH<sub>2</sub>). MS m/z: 178 (M<sup>+</sup>) 106, 91, 78, 50; IR (CHCl<sub>3</sub>) (ν<sub>max</sub>, cm<sup>-1</sup>): 1715.5, 1780.9 (C=O).

**1-Isopropyl-4-methyl-endo-bicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic anhydride (2):** α-Terpenine (1.0 g, 7.33 mmol) and maleic anhydride (0.72 g, 7.34 mmol) mp 50–52 °C; <sup>1</sup>H-NMR (400 MHz) (CDCl<sub>3</sub>): δ (ppm) = 6.067 (d, J = 8.5 Hz, 1H), 6.014 (d, J = 8.5 Hz, 1H), 3.80 (d, J = 6.5 Hz, 2H), 3.28 (d, J = 8.5, 1H), 2.91 (d, J = 8.5, 1H), 2.51 (septet, J = 6.8 Hz, 1H), 1.52 (m, 1H), 1.45 (s, 3H), 1.32 (m, 1H), 1.031 (d, J = 6.8 Hz, 3H), 0.958 (d, J = 6.9 Hz, 3H); <sup>13</sup>C-NMR (100 MHz) in CDCl<sub>3</sub>: δ (ppm) = 171.47 (C=O), 170.84 (C=O), 136.64 (CH), 135.89 (CH), 50.52 (CH), 47.85 (CH), 43.09 (C), 36.26 (C), 33.12 (CH<sub>2</sub>), 29.00 (C), 22.24 (CH<sub>2</sub>), 21.75 (CH<sub>3</sub>), 17.90 (CH<sub>3</sub>), 16.26 (CH<sub>3</sub>); MS m/z: 234 (M<sup>+</sup>) 163, 135, 119, 91; IR (CHCl<sub>3</sub>) (ν<sub>max</sub>, cm<sup>-1</sup>): 1770.6, 1834.2 (C=O).

**10-Isopropyl-8-methyl-4-oxa-tricyclo[5.2.2.0<sup>2,6</sup>]undec-8-ene-3,5-dione (3)** MS m/z: 234 (M<sup>+</sup>) 135, 119, 91.

**4-Methyl-4-aza-tricyclo[5.2.2.0<sup>2,6</sup>]undec-8-ene-3,5-dione (4):** MS m/z: 192 (M<sup>+</sup>) 113.

**1-Isopropyl-4,7-dimethyl-4-aza-tricyclo[5.2.2.0<sup>2,6</sup>]undec-8-ene-3,5-dione (5):** MS m/z: 247.1 (M<sup>+</sup>) 177, 113, 92, 77, 41.

**10-Isopropyl-4,8-dimethyl-4-aza-tricyclo[5.2.2.0<sup>2,6</sup>]undec-8-ene-3,5-dione (6):** MS m/z: 247.1 (M<sup>+</sup>) 177, 113, 92, 77, 41.

**1-Furan-2-ylmethyl-pyrrole-2,5-dione (7):** MS m/z: 177 (M<sup>+</sup>) 148, 120, 96, 82, 53.  
<sup>DEPT</sup>C NMR (90 MHz) 165.9 (C=O), 165.2 (C=O), 149.9 (C<sub>tetra</sub>), 142.3 (CH), 134.6 (CH), 131.8 (CH), 110.4 (CH), 108.2 (CH), 36.5 (CH<sub>2</sub>).

**1-Aminomethyl-4-methyl-10-oxa-4-aza-tricyclo[5.2.1.0<sup>2,6</sup>]decane-3,5-dione (8):** MS m/z: 209 (M<sup>+</sup>) 96, 53.

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