

STUDIES ON TANDEM ENE/INTRAMOLECULAR DIELS-ALDER REACTIONS¹

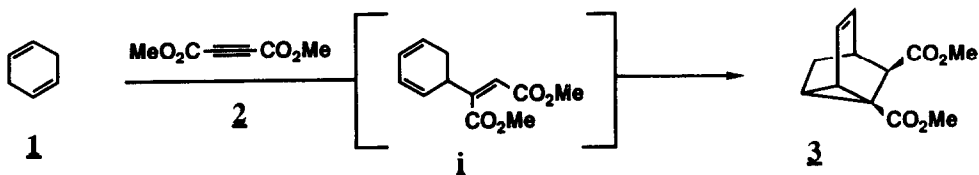
Raymond J. Giguere,* Andrew M. Namen,
 Blanca O. Lopez, Aravind Arepally, and Danielle E. Ramos
 Department of Chemistry, Mercer University, Macon, Georgia 31207

George Majetich* and Jean Defauw
 Department of Chemistry, The University of Georgia
 Athens, Georgia 30602

Summary: Tandem ene/intramolecular Diels-Alder reactions of 1,4-cyclohexadiene and mono- or di-activated acetylenes are optimized. Analogous reactions with disubstituted bicyclohexa-1,4-dienes regioselectively produce highly functionalized tetracyclic adducts.

Chemists have used commercial microwave ovens for a variety of purposes.² Last year we described how microwave heating substantially reduces the time necessary to complete Diels-Alder, ene, and Claisen reactions.³ Our interest in the development of thermal reactions using microwave heating led us to reinvestigate the reaction of 1,4-cyclohexadiene (**1**) and dimethylacetylene dicarboxylate (DMAD, **2**). This tandem ene/intramolecular Diels-Alder process was originally discovered by Alder and Bong in 1952, but proceeded in low yield [see Table 1].⁴ In 1966, the reaction was re-examined by Huebner and co-workers,⁵ although no yield was reported. Using microwave heating for six minutes, we have achieved this transformation in >80% yield.

Table 1. Optimization of the Alder-Bong Reaction



	<u>Thermal Conditions</u>	<u>Ene : Enophile</u>	<u>Time</u>	<u>Temp. °C</u>	<u>Yield</u>
1.	Literature ⁴	1.1 : 1	20 h	185	40 %
2.	Microwave	15 : 1	6 min	325 < 361	82 %
3.	Control	15 : 1	20 h	220	82 %
4.	Control	15 : 1	15 min	360	51 %

I. Di-Activated Enophiles:

The ene:enophile ratio influences the outcome of tandem ene/intramolecular Diels-Alder reactions. Using an equimolar ratio, the intermolecular Diels-Alder reaction of intermediate 1 with a second molecule of enophile predominates.⁶ We reasoned that this competing process would be suppressed by using an excess of diene. Indeed, a 15:1 ratio of ene:enophile, using either microwave or conventional heating, led to high yields of 3. Control experiments at 220°C required twenty hours to complete, while reactions at higher temperatures [$>320^{\circ}\text{C}$] for time periods comparable to microwave conditions suffered somewhat in yield (cf. entries 1 and 4, Table 1). A systematic study of the ene:enophile ratio as presented in Table 2 showed that for all practical purposes, an ene:enophile ratio of 10:1 provided tricyclic adduct 3 in high yield, though unidentified polymeric products (10-15%) were also formed.

Table 2: Comparative Parameters for the Reaction of 1,4-Cyclohexadiene and Dimethylacetylene Dicarboxylate using Microwave Heating.

	<u>Ene : Enophile Ratio</u>	<u>Time</u>	<u>Temp. °C</u>	<u>Yield of 3</u>
1.	2 : 1	5 min	300 < 317	48 %
2.	10 : 1	6 min	325 < 361	82 %
3.	15 : 1	6 min	325 < 361	82 %
4.	30 : 1	6 min	317 < 325	87 %

II. Mono-Activated Enophiles:

Analogous reactions with methyl propiolate, 3-butyne-2-one, and propiolic acid gave tricyclic adducts of unprecedented regioselectivity (4, 5 and 6, respectively). In contrast to the reaction of dimethylacetylene dicarboxylate 2 and 1, reaction of mono-activated acetylenes required higher temperatures [$>320^{\circ}\text{C}$] to complete in reasonable time; adducts are not obtained at lower temperatures. For example, control experiments failed to produce 4 even after 21 h at 235°C . However, addition of a catalytic amount of zinc chloride [20 mole %] affords adducts 4-6 in good yields at temperatures as low as 220°C within four hours.⁷ Reactions conducted with microwave heating under these conditions showed no improvement over the analogous non-catalyzed experiments. Weak Lewis acids, such as florisisil^{8a} or silica gel^{8b} fail, while treatment with stronger Lewis acids (SnCl_4 or $\text{BF}_3 \cdot \text{Et}_2\text{O}$) at 0°C generates mainly polymers.

Ene reactions of simple alkenes with unsymmetrical enophiles produce isomeric mixtures in which the regioisomer resulting from diene attack at the enophile's β -carbon predominates.⁹ Thus reaction of 1 with mono-activated acetylenes should have produced mainly adducts of type 7 (see Eq. 3). In contrast, adducts 4-6 clearly result from bond formation at the α -carbon of the enophile. Moreover, no evidence for the formation of type 7 regioisomers was observed.

Equation 1.

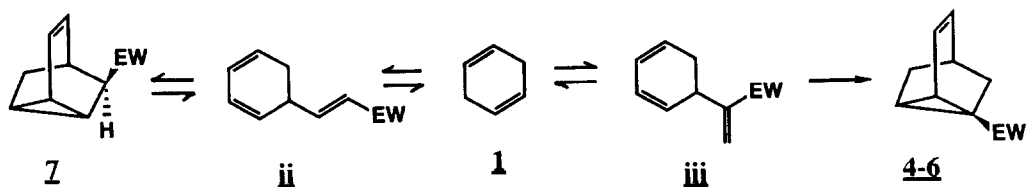
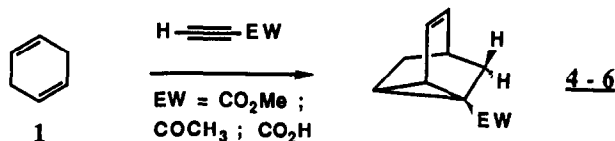


Table 3. Reactions of Mono-Activated Enophiles with 1,4-Cyclohexadiene



	Conditions ^{10a}		Time	Temp. (°C)	Yield
EW = CO ₂ Me (4) ^{6c}	1. Microwave	Neat	8 min	361 < 400	31%
	2. Control	Neat	21 h	230 - 235	0%
	3. Control	Neat	3 h	330	30%
	4. Microwave	ZnCl ₂	6 min	276 < 300	25%
	5. Control	ZnCl ₂	4 h	240	77%
EW = COMe (5) ^{6c}	1. Microwave	Neat	7 min	350 < 370	32%
	2. Control	Neat	3.5 h	335 - 340	36%
	3. Microwave	ZnCl ₂	6 min	276 < 300	32%
	4. Control	ZnCl ₂	18 h	220 - 230	68%
EW = CO ₂ H (6) ^{6c}	1. Control *	Neat	21 h	300	26%
	2. Control	ZnCl ₂	17 h	225	23%

* **CAUTION:** Excessive pressure exists even after cooling.

We believe that the tricyclic products obtained reflect the kinetic instability of the ene adducts under the superheating employed. Based on Alder's work,⁹ we assume that both intermediates ii and iii are formed, and that the normal ene adduct ii predominates. Either intermediate can undergo a retroene¹¹ or an intramolecular Diels-Alder reaction.¹²

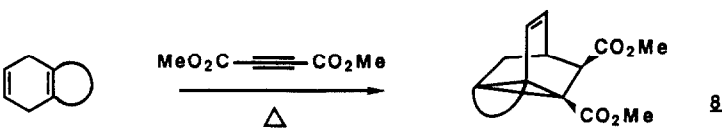
Literature precedent¹³ suggests that intermediate iii will undergo intramolecular Diels-Alder reaction more rapidly than ii, due to the nature of their respective dienophiles. Furthermore, once adducts 4-6 are formed, conjugation of the carbonyl group with the cyclopropane ring augments product stability, thus creating a thermodynamic bias for these isomers. Decomposition of ii via a retroene process and/or polymerization presumably leads to the observed product distribution.

III. Substituted Dienes:

Reaction of each of the dienes in Table 2 and DMAD afforded tetracyclic adducts of type 8 in moderate to high yields.^{6c} Products 9 and 11 result from regioselective addition at the tetrasubstituted double bond in the initial ene reaction.

In conclusion, tandem ene/intramolecular Diels-Alder reactions offer an efficient means of constructing highly functionalized carbocycles regioselectively. The use of microwave heating allows these reactions to be completed expeditiously.

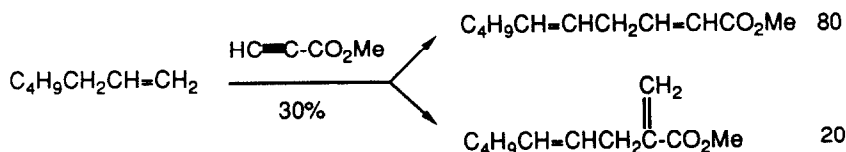
Table 4: Reaction of Bicyclic Dienes and Dimethylacetylene Dicarboxylate using Microwave Heating.

		
<u>Annulated Ring</u>	<u>Temperature (°C) ^{10b}</u>	<u>Yield</u>
9: { CH ₂ CH ₂ CH ₂ }	317 < 325	80%
10: { CH ₂ CH=CHCH ₂ }	300 < 317	65%
11: { CH ₂ C(OCH ₂ CH ₂ O)CH ₂ }	275 < 300	37%

Acknowledgments: RJG thanks The University of Georgia for a Visiting Lectureship (Summer, 1986) and Mercer University for receipt of a CLA Faculty Development Award (1986). AMN was a participant in The University of Georgia's Summer Undergraduate Research Program (1986).

References and Notes:

1. This work was presented in part at the 38th Southeastern Regional Meeting of the ACS in Louisville, KY, November, 1986; Abstract no. ORG 216, and at the 194th National Meeting of the ACS in New Orleans, LA, August, 1987; Abstract No. ORGN 114.
2. a) Chemistry in Britain, October, 1986, p 894. b) Industrial Chemical News, October, 1986, 7, No. 10, p 20. c) Kingston, H.M.; Jassie, L.B. Anal. Chem. **1986**, 58, 2534 and references therein. d) Gedye, R.; Smith, F.; Westaway, K.; Humera, A.; Baldisera, L.; Laberge, L.; Rousell, J. Tetrahedron Lett. **1986**, 27, 279.
3. Giguere, R.J.; Bray, T.L.; Duncan, S.M.; Majetich, G. Tetrahedron Lett. **1986**, 27, 4945.
4. Ph.D. Dissertation of C.-H. Bong, University of Cologne, West Germany, 1952.
5. Huebner, C.F.; Donoghue, E.; Dorfman, L.; Stuber, F.A.; Danieli, N.; Wenkert, E. Tetrahedron Lett. **1966**, 1185.
6. a) Spectroscopic data obtained for all new compounds were fully consistent with the assigned structures. b) Thermal reactions were typically run using one mmol of enophile and at high power setting in sealed tubes. The reaction of **1** to give **4** has been scaled up under microwave conditions (6 minutes) to one gram in 75% yield. c) New compound(s).
7. For examples of Lewis acid catalyzed ene reactions, see: Snider, B.B.; Deutsch, E.A. J. Org. Chem. **1983**, 48, 1822.
8. a) DeClercq, P.J.; Van Royen, L.A. Syn. Comm. **1979**, 9, 771. b) For use of silica gel as a Diels-Alder catalyst, see: Bartlett, P.D.; Blakeney, A.J.; Kimura, M.; Watson, W.H. J. Am. Chem. Soc. **1980**, 102, 1383.
9. Alder, K.; von Brachel, H. Liebigs Ann. Chem. **1962**, 651, 141.



10. a) All reaction were conducted with a ratio of ene:enophile of 10:1. b) All reaction were run for six minutes under microwave conditions³ in sealed tubes with an ene:enophile ratio of 15:1.
11. Agami, C.; Andrac-Taussing, M.; Justin, C.; Prevost, C. Bull. Soc. Chim. Fr. **1966**, 1195.
12. No direct or indirect evidence has been obtained for this conjecture.
13. Methyl methacrylate reacts with 9,10-dimethylantracene thirty times faster at +20°C than methyl trans-crotonate, an isomeric dienophile, cf. Schenck, G.O.; Kopp, H.R.; Kim, B.; Koerner, V.; Gastorf, E. Z. Naturforsch. **1965**, 206, 637.

(Received in USA 7 September 1987)