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Unprecedented Microwave Effects on the Cycloaddition of Fulvenes. A New Approach to the Construction of Polycyclic Ring Systems

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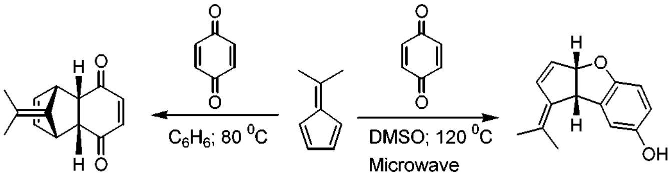
ABSTRACT



Novel cycloaddition reactions between fulvenes and various alkenes and alkynes are promoted by the use of microwave irradiation. These processes result in the formation of intriguing polycyclic ring systems such as those found in isobarbatene, alcyopterosin, and enokipodin A. Importantly, these reactions do not occur under conventional thermolytic conditions.

In 1986, Gedye and Giguere independently reported that organic reactions could be accelerated by microwave irradiation.[1] In general, microwave-assisted organic reactions (MOREs)[2] are faster and more efficient than their conventional counterparts.[3] The origin of this rate enhancement is debatable. Some have attributed it to a radiation effect known as the “microwave effect”,[4] while others refer to “hot spots”[5] generated within the medium. Regardless of the explanation, there are many documented cases of improvement or inversion of stereo-, regio-, or chemoselectivity[6] when microwaves are used instead of conventional heating.[7] While selectivity and yield may be affected, the microwave products retain the general backbone structure of the thermal products (e.g., cis/trans, syn/anti, endo/exo). Herein we report that for certain cycloadditions of fulvenes, the use of microwave irradiation instead of conventional heating leads to the formation of structurally unrelated products. *These results suggest that microwave irradiation can in fact alter the reaction pathway.*

Under conventional heating (C_6H_6, 80 °C, 8 h), 6,6-dimethylfulvene reacts with dimethyl maleate to afford the Diels−Alder adduct **3** in 84% yield (Table 1, entry 2).

During our studies of fulvene chemistry,[8] we subjected a DMSO solution of 6,6-dimethylfulvene and dimethyl maleate to microwave irradiation for 2 h.[9,10] Surprisingly, the tandem [6+4]−[4+2] cycloaddition products **1** and **2** were obtained

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(1) (a) Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, J. *Tetrahedron Lett.* **1986**, *27*, 279−282. (b) Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett.* **1986**, *27*, 4945−4948.

(2) (a) Majetich, G.; Wheless, K. *Microwave-Enhanced Chemistry*; American Chemical Society: Washington, DC, 1997; pp 455−505. (b) Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.* **1995**, *48*, 1665−1692. (c) Varma, R. S. *Pure Appl. Chem.* **2001**, *73*, 193−198. (d) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225−9283.

(3) For a recent example in the [6+4]-cycloaddition, see: Hong, B,-C.; Jiang, Y.-F.; Kumar, E. S. *Biorg. Med. Chem. Lett.* **2001**, *11*, 1981−1984.

(4) Langa, F.; Cruz, P. D. L.; Hoz, A. P. L.; Diaz-Ortiz, A.; Diez-Barra, E. *Contemp. Org. Synth.* **1997**, *4*, 373−386.

(5) Stuerga, D.; Gaillard, P. *Tetrahedron* **1996**, *52*, 5505−5510.

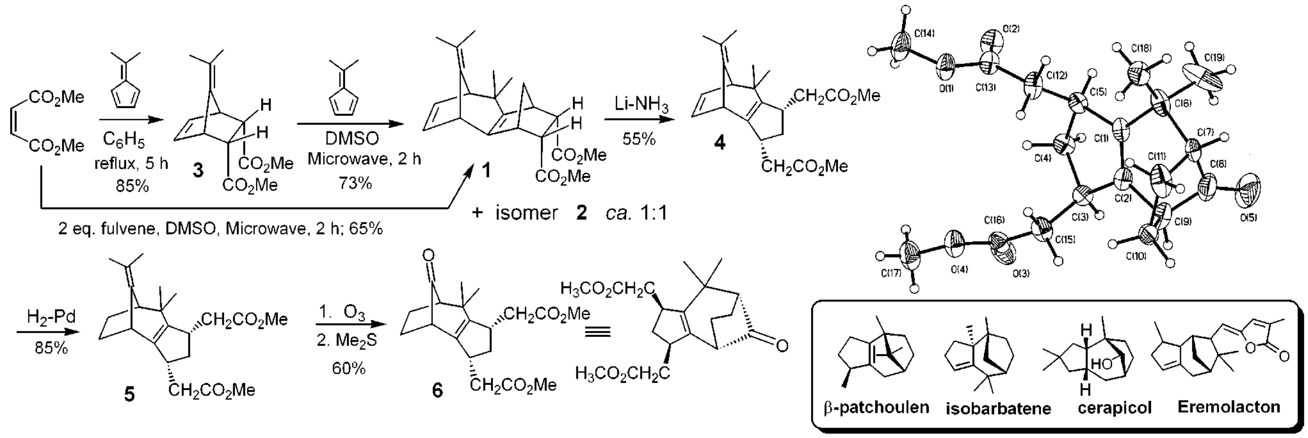
(6) (a) Forfar, I.; Cabildo, P.; Claramunt, R. M.; Elguero, J. *Chem. Lett.* **1994**, 2079−2080. (b) Almena, I.; Diaz-Ortiz, A.; Diez-Barra, E.; Hoz, A.; Loupy, A. *Chem. Lett.* **1996**, 333−334.

(7) Bose, A. K.; Banik, B. K.; Manhas, M. S. *Tetrahedron Lett.* **1995**, *36*, 213−216.

(8) For previous papers in this series, see: (a) Hong, B.-C.; Shen, I. C.; Liao, J. H. *Tetrahedron Lett.* **2001**, *42*, 935−938. (b) Hong, B.-C.; Chen, Z.-Y.; Chen, W.-H. *Org. Lett.* **2000**, *2*, 2647−2649 and references therein.

10.1021/ol017304q CCC: $22.00

Scheme 1



in 30% (Table 1, entry 1). In fact, the combined yield of **1** and **2** increased to 65% when 2 equiv of 6,6-dimethylfulvene were used. Reductive cleavage of **1** in the presence of Li/NH$_3$ (55% yield) followed by selective hydrogenation of the disubstituted alkene (H$_2$, Pd−C) provided diester **5** in 85% yield. Ozonolysis of **5** afforded ketoester **6** in 60% yield. The tricyclo[5.3.0.1^{2,5}]alkane structure of **6** was unambiguously assigned using single-crystal X-ray analysis (Scheme 1). As shown in Scheme 2, a plausible mechanism for the formation of **1** under microwave irradiation involves the competitive and reversible formation of Diels−Alder adduct **3** and facile dimerization of fulvene via a [6+4]-cycloaddition pathway to give the dimer **7** (pathway A).[11] Subsequently, [4+2]-cycloaddition of **7** with dimethyl maleate occurs to generate adducts **1** and **2**.

Alternatively, dimerization of fulvene via [4+2]-cycloaddition affords adduct **8**, which can be transformed to dimer **7** by a [3,3]-sigmatropic rearrangement and a 1,5-hydrogen shift (pathway **B**). As a third alternative, an acid-catalyzed Wagner−Meerwein rearrangement pathway can be envisaged (pathway **C**). Accordingly, acid-catalyzed reaction of **3** will generate norbornyl cation **9** and could lead to **10** by a 1,2-alkyl shift. Cation **10** would then undergo the [4+3]-cycloaddition with fulvene to provide **11** and **12**. However, we have found that treatment of **3** with acid (PTSA, HCl, or H$_2$SO$_4$) in the presence of dimethylfulvene in refluxing C$_6$H$_6$ leads to complete recovery of the starting materials. In addition, inclusion of acid in the microwave irradiation reaction of **3** with dimethylfulvene did not result in a rate enhancement during the formation of **1** and **2**. These observations help rule out pathway **C**. We also reacted a series of homologous alkenes and alkynes with dimethylfulvene using microwave heating (Table 1). Interestingly, different mechanistic pathways are followed in these processes. For example, reaction of 6,6-dimethylfulvene with maleic anhydride under microwave conditions gave the [4+2]-cycloadduct **13**, an analogue of the natural product alcyopterosin[20] (Table 1, entry 3).[21] Maleic anhydride appears to add across the C-1 methyl and C-6 atom of the fulvene. This is the first example of a fulvene reacting in such a manner to afford a hydrindane system. In addition, reaction of maleic anhydride with dimethylfulvene under conventional heating has been reported to give the Diels−Alder adduct **14** in 67% yield (Table 1, entry 4). A possible mechanism for the formation of **13** involves microwave-induced isomerization of 6,6-dimethylfulvene to 2-isopropenyl-cyclopenta-1,3-diene followed by trapping with maleic anhydride via [4+2]-cycloaddition. Reaction of 6,6-dimethylfulvene with 2(5*H*)-furanone under microwave conditions afforded adducts **15** and **16** in a 1:2 ratio. These products may also arise by

Scheme 2

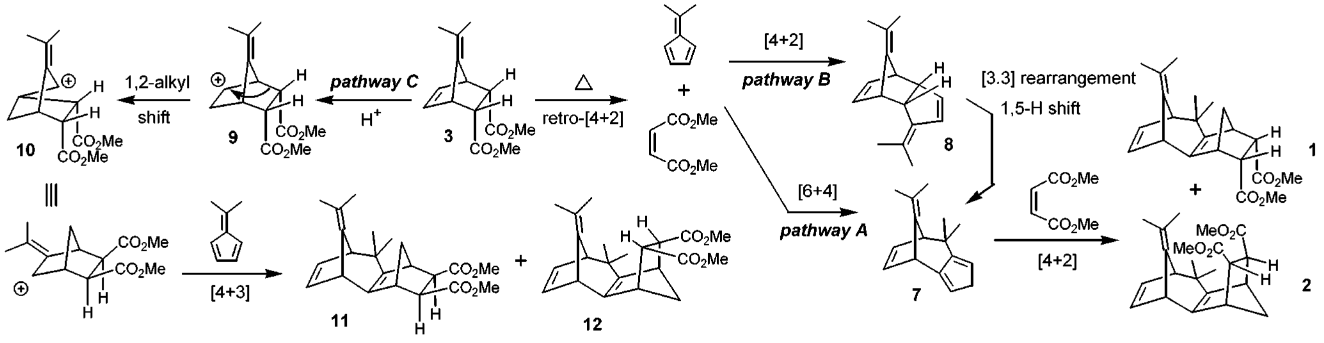
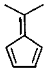
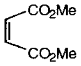
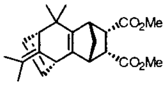
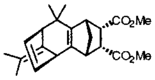
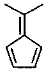
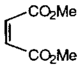
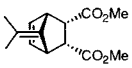
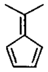
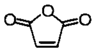
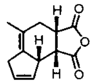
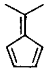
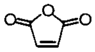
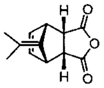
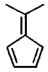
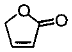
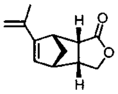
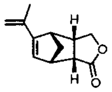
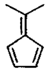
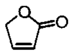
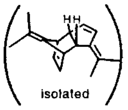
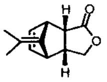
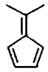
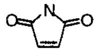
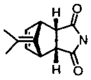
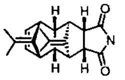
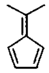
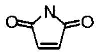
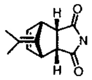
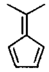
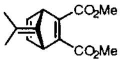
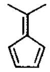
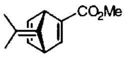
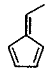
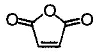
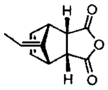
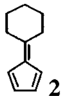
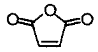
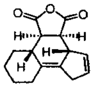
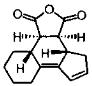
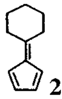
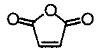
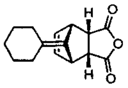
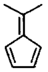
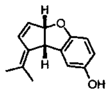
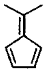
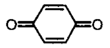
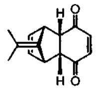


Table 1. Reactions of Fulvenes with Alkenes or Alkynes

entry	fulvene	substrate	product	time (min)	temp (°C)	method	yield[a] (%)
1			 **1** (1 : 1) **2** 	60	150	A	30 65[b]
2			 **3**	480 60	80 150	B C	84[12,e] 65
3			 **13**	30	150	A	53
4			 **14**	2880 30	80 150	B C	67[13] ~0[f]
5			 **15** (1 : 2) **16** 	30 30	150 150	A C	55 3
6			 isolated  Not Observed **17**	4320	80	B	~0[c]
7			 **18** (3 : 1) **19** 	30	150	A	74 80[d]
8			 **18**	1440 30	110 150	B C	89[14] 75
9		MeO$_2$C—≡—CO$_2$Me	 **20**	60 480	150 80	A B	63 89[15,e]
10		H—≡—CO$_2$Me	 **21**	60 480	150 110	A B	58 50[16]
11			 **22**	30 480	120 80	A B	78 56[17,e]
12	 **23**		 **24** (1 : 1) **25** 	30	150	A	62
13	 **23**		 **26**	480 30	80 150	B C	68[18,e] ~0[f]
14			 **27**	10	120	A	60
15			 **28**	120 10	80 120	B C	70[19] ~0[f]

[a] Isolated yield based on starting fulvene. [b] Two equivalents of fulvene were used. [c] Recovered 50% of starting fulvene and 25% of fulvene dimer. [d] Yield for **19**; 2 equiv of fulvene were used. [e] From this work; no yield was reported in the literature. [f] Complicated mixtures. Method A: Microwave irradiation. Method B: Conventional oil bath heating in C_6H_6. Method C: Conventional oil bath heating in DMSO.

initial isomerization of the fulvene to 2-isopropenylcyclopenta-1,3-diene, followed by trapping with furanone via [4+2]-cycloaddition across C-3 and C-5 of fulvene, i.e., C-4 and C-6 of 2-isopropenyl-cyclopenta-1,3-diene. Reaction of 6,6-dimethylfulvene with 2(5*H*)-furanone under conventional heating conditions afforded fulvene dimerization exclusively (Table 1, entry 6). Microwave reaction of 6,6-dimethylfulvene with maleimide yielded **18** and **19** in 74% yield and in a 3:1 ratio (Table 1, entry 7). In the presence of 2 equiv of dimethylfulvene, the yield of **19** increased to 80%. The structure of **19** was determined by X-ray analysis (Figure 1). Reaction of dimethylfulvene with maleimide, under conventional heating conditions, gave adduct **18** in 89% yield (Table 1, entry 8), while reaction of fulvene with dimethyl

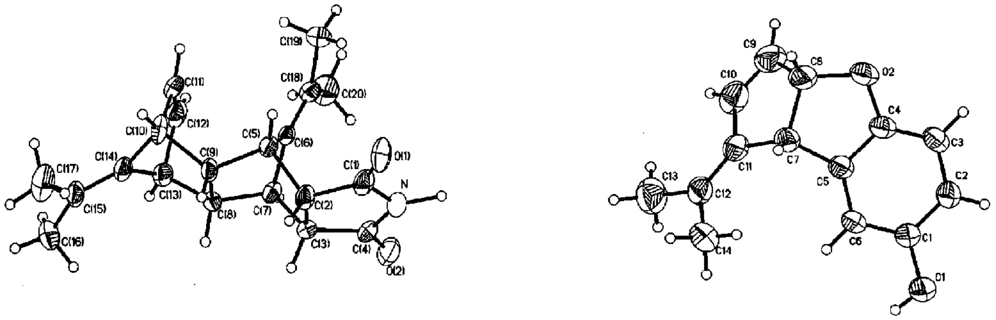


Figure 1. ORTEP plots for X-ray crystal structures of **19** and **27**.

acetylenedicarboxylate or methyl propiolate gave the [4+2]-adducts **20** and **21**, respectively, under both microwave irradiation and conventional heating conditions (Table 1, entries 9 and 10).

Reaction of 6-methylfulvene and maleic anhydride also gave the [4+2]-adduct **22** under both microwave and conventional heating conditions (Table 1, entry 11). The reason for the dramatic differences seen in reactions of 6-methylfulvene and 6,6-dimethylfulvene (Table 1, entry 3) is not clear. This may be a result of the lower reactivity of methylfulvene by isomerization to 2-vinyl-cyclopenta-1,3-diene. Reaction of fulvene **23** with maleic anhydride afforded adducts **24** and **25** in a 1:1 ratio, which is different from the results produced by conventional heating (Table 1, entries 12 and 13). A similar outcome is seen in the reaction of 6,6-dimethylfulvene with maleic anhydride (Table 1, entries 3 and 4). Reaction of 6,6-dimethylfulvene and benzoquinone under microwave conditions afforded the hetero-[2+3]-adduct **27** in a 60% yield (Table 1, entry 14). Adduct **27** is a structural analogue of aplysin and pannellin[22] and differs completely from the well-known thermal Diels−Alder cycloaddition products of fulvenes and benzoquinone (Table 1, entry 15).

In summary, the processes are facile methods for the synthesis of densely functionalized polycyclic ring systems. The study further demonstrates that microwave irradiation not only enhances the rates of reactions but can also effect reactions by giving rise to products that do not form under conventional thermolytic conditions. Mechanistic studies and applications of this work to the synthesis of naturally occurring compounds are currently under active investigation.

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Supporting Information Available: Crystallographic information files (CIF) for **6**, **19**, and **27**, experimental procedures, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Focused microwave irradiation was carried out at atmospheric pressure with a Synthewave S402 Prolabo microwave reactor (300 W, monomode system, 10 mL reactors). The apparatus has a quartz reactor, visual control, PC-controlled 300 W irradiation, and infrared temperature measurement with continuous feedback control.

(10) **Typical Procedure for Synthesis of 1 and 2.** A mixture of 6,6-dimethylfulvene (650 mg, 6 mmol), dimethyl maleate (420 mg, 2.9 mmol), and DMSO (5 mL) were placed in a 10 mL quartz vial and subjected to programmed microwave irradiation at 30 W for 120 min. After a period of 2−3 min, the temperature reached a plateau of 150 °C where it remained throughout the reaction. After cooling, the solution was concentrated and the residue was subjected to flash column chromatography (10% EtOAc−hexane, $R_f = 0.32$ in 15% EtOAc−hexane) to give the adducts **1** and **2** as colorless liquids (**1**: 328 mg, 32% yield; **2**: 341 mg, 33% yield).

(11) A similar tricyclo[6.2.1.0^{2,6}]undecane structure, fulvene dimer, was proposed as the first step ([6+4]-dimerization) in the trimerization of 6,6-dimethyl fulvene; see: Uebersax, M.; Neuenschwander, M.; Engel, P. *Helv. Chim. Acta* **1982**, *65*, 89−104.

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