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Novel [6 + 2] Cycloaddition of Fulvenes with Alkenes: A Facile Synthesis of the Anislactone and Hirsutane Framework

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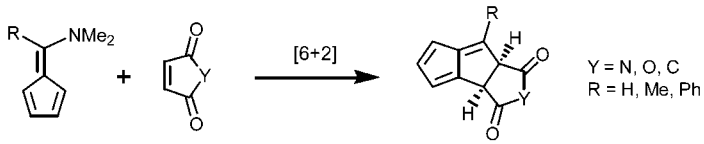
ABSTRACT



In contrast to the Diels–Alder reaction of fulvenes and various alkenes, 6-aminofulvenes react with maleic anhydride (or maleimide) to give [6 + 2] cycloaddition adducts, constituting an efficient and novel route to pentaleno[1,2-*c*]furan, pentaleno[1,2-*c*]pyrrole, and cyclopenta[*a*]-pentalene skeleton.

Cycloadditions of fulvenes (e.g., [4 + 3], [2 + 2], [4 + 2], [2 + 4], [6 + 4]) provide powerful synthetic approaches to various polycyclic systems and natural products.[1] In addition to these versatile reactions, we recently reported a novel hetero [6 + 3] cycloaddition of fulvenes for the synthesis of 11-oxasteroids.[2] In conjunction with our continuing efforts in fulvene chemistry,[3] we have now developed a [6 + 2] cycloaddition using 6-aminofulvenes and maleic anhydride (or maleimide) for the preparation of pentaleno[1,2-*c*]furans and pentaleno[1,2-*c*]pyrroles. These compounds constitute the basic skeleton of many natural products such as anislactone A,[4] anislactone B,[5] merrilactone A,[6] merrilactones B and C,[7] and various other important synthetic intermediates.[8]

[6 + 2] cycloadditions of cycloheptatriene, vinylcyclobutanones, or azepine with alkenes are well precedented.[9]

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(9) (a) Rigby, J. H.; Kondratenko, M. A.; Fiedler, C. *Org. Lett.* **2000**, *2*, 3917−3920. (b) Wender, P. A.; Correa, A. G.; Sato, Y.; Sun, R. *J. Am. Chem. Soc.* **2000**, *122*, 7815−7816. (c) Chaffee, K.; Huo, P.; Sheridan, J. B.; Barbieri, A.; Aistars, A.; Lalancette, R. A.; Ostrander, R. L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1995**, *117*, 1900−1907. (d) Schmidt, T.; Bienewald, F.; Goddard, R. *J. Chem. Soc., Chem. Commun.* **1994**, 1857−1858. (e) Fischler, I.; Grevels, F. W.; Leitich, J.; Ozkar, S. *Chem. Ber.* **1991**, *124*, 2857−2861. (f) Mach, K.; Antropiusova, H.; Petrusova, L.; Hanus, V.; Turecek, F.; Sedmera, P. *Tetrahedron*, **1984**, *40*, 3295−3302.

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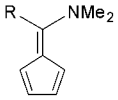
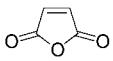
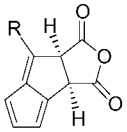
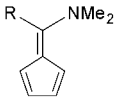
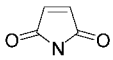
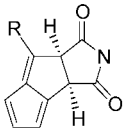
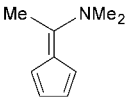
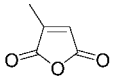
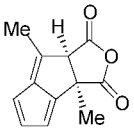
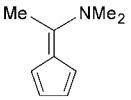
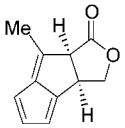
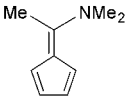
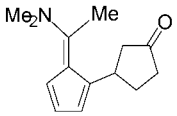
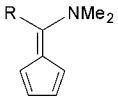
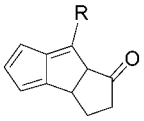
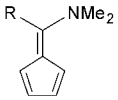
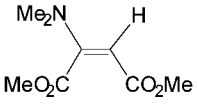
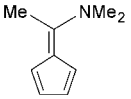
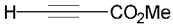
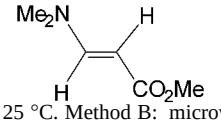
Table 1. Reaction of Alkenes and Alkynes with Fulvenes

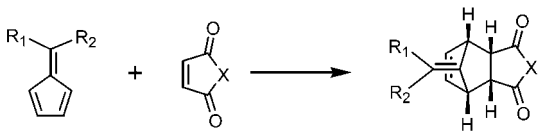
entry	fulvene	substrate	product		method	time (min)	yield (%)[a]
1				**2**. R = Me	A	30	81
				3. R = Ph	A	60	73
				4. R = H	A	480	70
2				**5**. R = Me	A	120	75
				6. R = Ph	A	480	66
				7. R = H	A	480	65
3				**8**	B	30	63
4				**9**	A	2880	
					B	2880	0
					C	240	
5				**10**	D	15	56
6				**11**. R = Me	E	240	65
				12. R = H	F	45	75
7	 R = Me, Ph, H			**13**	A	R = Me, 180	85
					A	R = Ph, 180	84
					A	R = H, 180	87
8				**14**	A	480	65

[a] Isolated yield based on starting fulvene. Method A: C_6H_6, 25 °C. Method B: microwave irradiation at 10 W in DMF, 120 °C. Method C: microwave irradiation at 30 W in DMSO, 150 °C. Method D: cat. $BF_3{\cdot}OEt_2$, −78 °C, THF. Method E: 1 equiv of $BF_3{\cdot}OEt_2$, reflux, THF. Method F: 1 equiv of $BF_3{\cdot}OEt_2$, 50 °C, THF.

However, like cycloheptatriene, the [6 + 2] cycloaddition of fulvene has received little attention.[10,11]

Many papers have reported that, in general, fulvene reacts with maleic anhydride to give the [4 + 2] cycloaddition adduct,[12] (Scheme 1). In contrast, we have found that reaction of 6-dimethylaminofulvene (**1**) with maleic anhydride gave the intriguing pentalene derivative **2**, (Scheme 2). To the best of our knowledge, this is the first reported synthesis of a pentaleno[1,2-*c*]furan system via a [6 + 2] cycloaddition of fulvene. In our hands, addition of 6-dimethylaminofulvene (**1**) to a solution of maleic anhydride in benzene at 25 °C

Scheme 1



R_1 = CH_3, Ph, H, OTMS, 2-pyridyl-, 2-furanyl, 2 or 3-thiophenyl, CH_2OR, CH=CHPh, $-CH_2(CH_2)_3CH_2-$

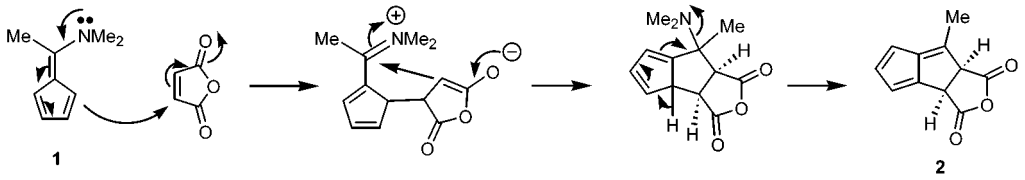
R_2 = CH_3, Ph, H, 2-pyridyl-, 2-furanyl, 2 or 3-thiophenyl, $-CH_2(CH_2)_3CH_2-$

X = O, N

(10) For the intramolecular reaction of 6-(5-dialkylamino-4-pentyl)fulvene and enamines, see: Wu, T. C.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 5308−5309.

(11) For addition of 1,3-di-*tert*-butyl-6-dimethyl-aminofulvene to alkynes, see: Hafner, K.; Suda, M. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 314−315.

Scheme 2



for 30 min provided the pentalene derivative **2** in 81% yield as the only isolable product, (entry 1, Table 1). The structure of **2** was assigned on the basis of IR, ^{1}H and ^{13}C NMR, COSY, DEPT, HMQC, HMBC, MS, and HRMS analysis. This dramatic difference in the chemoselectivity between 6-dimethylaminofulvene (**1**) and alkylfulvenes may be due to an increase in the electron density of the 6-dimethylaminofulvene π-system. The formation of **2** may be rationalized by the stepwise mechanism shown in Scheme 2. Initial addition of **1** to maleic anhydride generates the zwitterionic intermediate. This is followed by nucleophilic attack at the C-6 position of fulvene to give the pentalene derivative **2**.

A series of homologous maleic anhydrides and maleimide were then reacted with various aminofulvenes to give the corresponding products **3**−**9** (entries 1−4, Table 1).[13] Reaction of **1** with maleimide afforded adduct **5**. The structure of **5** was unambiguously assigned by single-crystal X-ray analysis (Figure 1).[14]

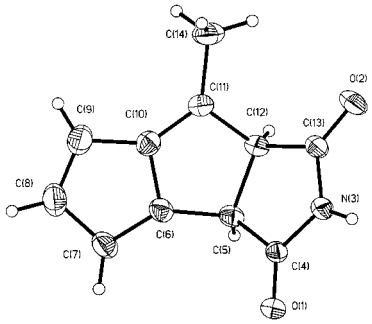


Figure 1. ORTEP plots for X-ray crystal structures of **5**.

Reaction of various aminofulvenes with maleic anhydride and maleimide gave similar adducts **3**,**4** and **6**,**7** in good yields (entries 1 and 2, Table 1). Methyl maleic anhydride and **1** did not react in benzene at reflux; however, microwave irradiation provided adduct **8** in 63% yield (entry 3, Table 1). Unfortunately, we could not get γ-butyrolactone and **1** to react. In this case, the use of Lewis acids such as BF_3·Et_2O, $AlCl_3$, $EtAlCl_2$, $TiCl_4$, etc. gave decomposition of fulvene and no other product (entry 4, Table 1). Reaction of the methylaminofulvene with 2-cyclopentenone did not give any reaction either (starting materials were recovered). However, the 1,4-alkylation adduct **10** (ca. 1:1 ratio of regioisomers) was obtained in the presence of catalytic amounts of BF_3·Et_2O at −78 °C (entry 5, Table 1).

Interestingly, reaction of aminofulvene and 2-cyclopentenone with 1 equiv of BF_3·Et_2O (reflux, 240 min) afforded the tricyclic product **11** in 65% yield (entry 6, Table 1). Milder conditions could be used for 6-dimethylaminofulvene (1 equiv of BF_3·Et_2O, 50 °C) to provide the tricyclic product **12** in 75% yield (entry 6, Table 1). Cyclopenta[*a*]pentalene adducts **11** and **12** are structural analogues of biologically active natural products incarnal,[15] pleurotellol,[16] ceratopicanol,[17] and hypnophilin.

Reaction of dimethylaminofulvene with dimethyl acetylenedicarboxylate and methyl propiolate provided the dimethylamine adducts **13**[18] and **14**[19] (entries 7 and 8, Table 1). A plausible mechanism for this transformation is shown in Scheme 3. Michael addition of the fulvene amino group to the triple bond followed by hydrolysis during workup affords 2-dimethylaminomaleic acid dimethylester **13**.

In summary, a novel one-pot [6 + 2] cycloaddition of fulvenes to maleic anhydride, maleimide, and cyclopentenone has been reported. This constitutes a novel methodology for

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(13) All new compounds were characterized by full spectroscopic (^{1}H and ^{13}C NMR, DEPT, IR, MS, and HRMS) data. Most of them have COSY and HMQC data. Yields refer to spectroscopically and chromatographically homogeneous (>95%) materials.

(14) Crystallographic data for **5**: $C_{11}H_9NO_2$, M = 187.19, monoclinic, space group $P2_1/c$, T = 293 K, a = 13.6525(16) Å, b = 8.1225(9) Å, c = 8.4007(10) Å, β = 97.529(2)°, V = 923.54(19) Å^3, Z = 4, D = 1.346 g/cm^3, λ (Mo Kα) = 0.71073 Å, 5577 reflections collected, 2114 unique reflections, 127 parameters refined on F^2, R = 0.0661, w$R_2[F^2]$ = 0.2174 [1823 data points with $F^2 > 2\sigma(F^2)$].

(15) Isolated from *Gloeostereum incarnatum*, with antibacterial activity; see: Takazawa, H.; Kashino, S. *Chem. Pharm. Bull.* **1991**, *39*, 555−557.

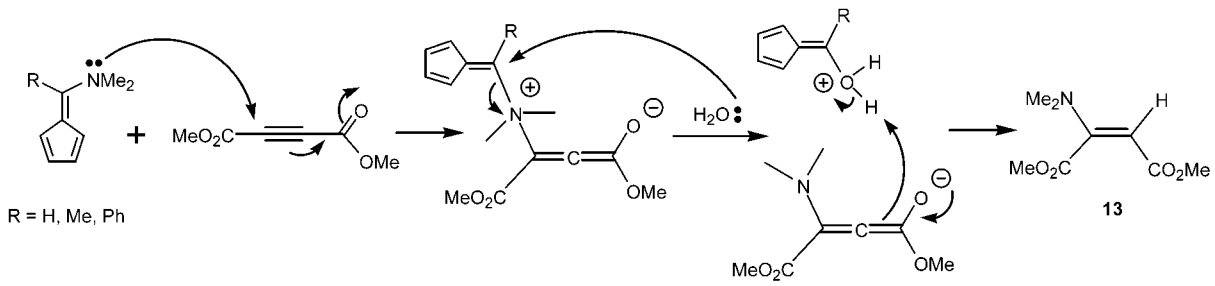
(16) Isolated from *Pleurotellus hypnophilus*, with antibacterial activity; see: Giannetti, B. M.; Steffan, B.; Steglich, W.; Kupka, J.; Anke, T. *Tetrahedron* **1986**, *42*, 3587−3593.

(17) Isolated from the fungus *Ceratocystis piceae* Ha 4/82; see: Hanssen, H.-P.; Abraham, W.-R. *Tetrahedron* **1988**, *44*, 2175−2180.

(18) (a) Schwan, A. L.; Warkentin, J. *Can. J. Chem.* **1988**, *66*, 1686−1694. (b) Guzman, A.; Romero, M.; Talamas, F. X.; Villena, R.; Greenhouse, R.; Muchowski, J. M. *J. Org. Chem.* **1996**, *61*, 2470−2483.

(19) Roessler, U.; Blechert, S.; Steckhan, E. *Tetrahedron Lett.* **1999**, *40*, 7075−7078.

Scheme 3



the synthesis of pentaleno[1,2-*c*]furans (anislactone and merrilactone skeletons), cyclopenta-[*a*]pentalenes (hirsutane skeleton), and pentaleno[1,2-*c*]pyrroles. We are currently pursuing the application of this methodology to the synthesis of various natural products.

Acknowledgment. We are grateful to Dr. Sepehr Sarshar for valuable discussions. Financial support from National Science Council and National Health Research Institute are gratefully acknowledged.

Supporting Information Available: Crystallographic information files (CIF) for **5** and experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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