Some Preparatively Useful [4 + 2]Cycloadditions of 6,6-Diphenylfulvene

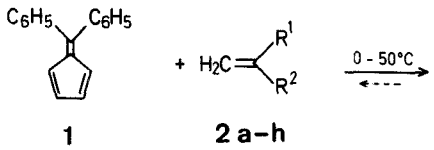
Herbert SIEGEL

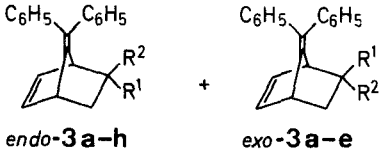
Hauptlaboratorium der Hoechst AG, D-6230 Frankfurt 80, Federal Republic of Germany

During our search for new, pharmacologically interesting compounds, we investigated the [4 + 2]cycloaddition reaction of 6,6-diphenylfulvene (**1**) to obtain less common

bicyclo[2.2.1]heptane derivatives. Although much work has been done on fulvenes[1], their preparative use in the Diels-Alder reaction is not well elaborated. According to some older reports[1,2], fulvenes appeared to be not very reactive diene components and needed rather long reaction times to give adducts that can easily undergo a retro-Diels-Alder reaction[3]. This and the fact that fulvenes readily undergo dimerization and oligomerization[2,4] as well as the several cycloaddition pathways[5] possible probably led to the low interest in the use of fulvenes for preparative diene synthesis.

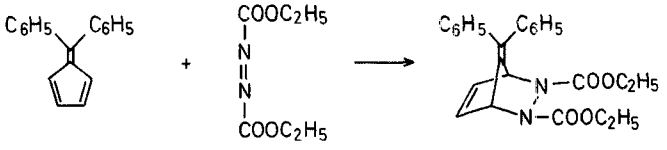
In spite of these facts, we have now found that a variety of useful synthetic intermediates can be obtained from 6,6-diphenylfulvene (**1**) in high yields and in reasonable reaction times under appropriate conditions by simple [4 + 2]-cycloaddition. The reaction takes place at room temperature or at slightly elevated temperatures within a few hours or a few days, when 6,6-diphenylfulvene (**1**) is allowed to stand in the presence of an excess of the dienophile **2** to give *exo-*/*endo-* or both the isomers of the adduct **3** (*exo-*/*endo-* is related to the substituent R^1). The products are stable enough to be isolated. Usually the *endo*-isomer predominates and in the case of crystalline adducts, the isomers can be separated by fractional crystallization from different solvents. Oily products are purified by column chromatography on silica gel using cyclohexane/ethyl acetate (5 : 1) as eluent (Table).





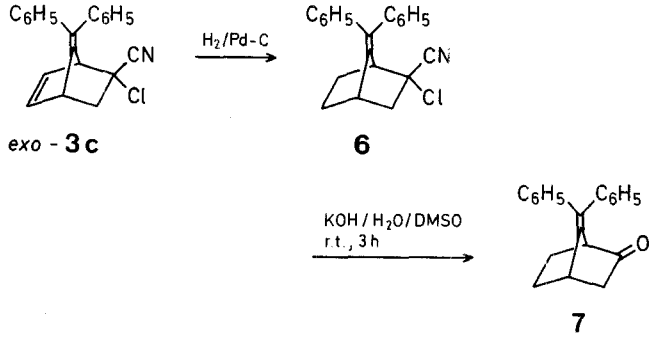
2,3	R^1	R^2
a	-COOH	H
b	$-COOCH_3$	H
c	-CN	Cl
d	-CN	H
e	$-COOC_2H_5$	$-P(=O)(OC_2H_5)_2$
f	$-C(=O)-CH_3$	H
g	$-NO_2$	H
h	$-S(=O)-C_6H_5$	H

The addition proceeds well for electron-deficient olefins. The ketene equivalents[6], α-chloroacrylonitrile (**2c**) or nitroethylene (**2g**) gave high yields, while the acetylene equivalent[7], phenyl vinyl sulphoxide (**2h**), a less strong dienophile, did not give more than 10% of adduct even after prolonged heating. 1,2-Substituted olefins like cinnamic acid did not react. Heterodienophiles[8] like nitrosobenzene or *N*-sulfinylaniline also did not give the adducts, which might be explained by the ring strain in the expected products. On the other hand the reaction with diethyl azodicarboxylate (**4**) to give the adduct **5** shows that the addition of heterodienophiles in principle is possible.



The assignment of stereochemistry of the reaction products is done by means of their ^{1}H-N.M.R. spectra. The *exo*-proton in the 2-position of the *endo*-isomers is less shielded than the *endo*-hydrogen atom of the *exo*-isomers and therefore is shifted more downfield. The *exo*-position of the cyano group in the major isomer of the adducts **3c** was assigned by comparison of their spectra with those of the addition products of α-chloroacrylonitrile (**2c**) to furan[9]. The structure assignment for **3e** was done by ^{31}P-N.M.R., assuming *exo*-**3e** (δ = 24.55 ppm) appears at higher field than *endo*-**3e** (δ = 25.45 ppm).

As an example for the synthetic utility of the products prepared, the conversion of **3c**[10] to the bicyclic ketone **7** shall be mentioned. Hydrogenation of **3c** at ambient temperature and pressure led in quantitative yield to the nitrile **6**, which, on treatment with potassium hydroxide in aqueous dimethyl sulfoxide[11], gave **7** in 91% yield.



***exo-* and *endo*-2-Chloro-2-cyano-7-diphenylmethylenebicyclo-[2.2.1]hept-5-ene (3c); Typical Procedure:**

A mixture of 6,6-diphenylfulvene (**1**; 23.0 g, 0.1 mol) and α-chloroacrylonitrile (**2c**; 17.5 g, 0.2 mol) is allowed to stand for 5 days at room temperature to give a reddish oil. Removal of excess of **2c** in vacuo leaves 32 g of the crude product, which is repeatedly crystallized from isopropanol to afford *exo*-**3c**; yield: 25.2 g (80%); m.p. 132°C.

The *endo*-product is obtained from the mother liquor by crystallization from cyclohexane; yield: 3.9 g (12%); m.p. 138°C (total yield of adducts: 92%).

7-Diphenylmethylene-bicyclo[2.2.1]hept-5-en-2-one (6):

A solution of the *exo*-adduct **3c** (18.2 g, 57 mmol) in tetrahydrofuran (150 ml) is hydrogenated at ambient temperature and pressure using 5% palladium on charcoal (500 mg) as catalyst. The mixture is filtered after the hydrogenation is over, evaporated to dryness and the residue is recrystallized from ethanol to give pure **6**; yield: 17.6 g (96%); m.p. 90°C.

$C_{21}H_{18}ClN$	calc.	C 78.86	H 5.67	Cl 11.08	N 4.38
(319.8)	found	78.90	5.40	11.20	4.40

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.50–2.50 (m, 5H); 1.97 (d, 1H, J = 12 Hz); 2.83 (ddd, 1H, J = 12 Hz, 4 Hz, 3 Hz); 2.92 (d, 1H, J = 3 Hz); 7.00–7.50 ppm (m, 10 H).

7-Diphenylmethylene-bicyclo[2.2.1]heptan-2-one (7):

To a solution of **6** (17.5 g, 55 mmol) in dimethyl sulfoxide is added a solution of potassium hydroxide (7.8 g, 139 mmol) in water (30 ml).

Table. Reaction of 6,6-Diphenylfulvene (**1**) with Dienophiles **2**

Dienophile	Product	Reaction conditions: time [days]/temp. [°C]/ratio of **1** : **2**	Yield [%][a] (*endo*-/*exo*-)	m.p. [°C] (solvent)	Molecular Formula[b] or Lit. m.p. [°C]	I.R. (CCl_4)[c] ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS)[d] δ [ppm]
2a	*endo*-**3a**	5/r.t./1 : 5	87 (4.2 : 1)	185° (ethanol)	170°[2]	2300–3500, 1695	1.63 (dd, J = 12 Hz, J = 5 Hz, 1H); 2.20 (ddd, J = 12 Hz, J = 9 Hz, J = 5 Hz, 1H); 3.20 (dt, J = 9 Hz, J = 5 Hz, 1H); 3.45 (m, 1H); 3.76 (m, 1H); 6.27 (dd, J = 6 Hz, J = 3 Hz, 1H); 6.47 (dd, J = 6 Hz, J = 3 Hz, 1H); 7.00–7.45 (m, 10H)
	exo-**3a**			146° (cyclohexane)	$C_{21}H_{18}O_2$ (302.4)	2300–3500, 1695	1.62 (dd, J = 11 Hz, J = 3 Hz, 1H); 2.20–2.54 (m, 2H); 3.38–3.65 (m, 2H); 6.43 (t, J = 2 Hz, 2H); 7.00–7.45 (m, 10H)
2b	*endo*/*exo*-**3b**	40[e]/50°/1 : 3	96 (1.8 : 1)[f]	oil	$C_{22}H_{20}O_2$ (316.4)	1710	1.50 (dd, J = 12 Hz, J = 10 Hz); 1.60 (dd, J = 12 Hz, J = 4 Hz); 2.00–2.50 (m); 3.12 (dt, J = 10 Hz, J = 4 Hz); 3.35–3.80 (m, 2H); 3.50 (s, *exo*-CH_3); 3.55 (s, *endo*-CH_3); 6.15–6.50 (m, 2H); 7.00–7.45 (m, 10H)
2c	*endo*-**3c**	5/r.t./1 : 2	92 (1 : 6.6)	138° (cyclohexane)	$C_{21}H_{16}ClN$ (317.8)	2340	2.40 (d, J = 13 Hz, 1H); 2.57 (dd, J = 13 Hz, J = 4 Hz, 1H); 3.61 (m, 1H); 3.84 (m, 1H); 6.48 (dd, J = 6 Hz, J = 3 Hz, 1H); 6.73 (dd, J = 6 Hz, J = 3 Hz, 1H); 7.05–7.45 (m, 10H)
	exo-3c			132° (isopropanol)	$C_{21}H_{16}ClN$ (317.8)	2330	1.88 (d, J = 13 Hz, 1H); 2.96 (dd, J = 13 Hz, J = 4 Hz, 1H); 3.60 (m, 1H); 3.96 (m, 1H); 6.36 (dd, J = 6 Hz, J = 3 Hz, 1H); 6.68 (dd, J = 6 Hz, J = 3 Hz, 1H); 7.00–7.50 (m, 10H)
2d	*endo*-**3d**	7/r.t./1 : 5	91 (1.6 : 1)	142° (cyclohexane)	137°[2]	2335	1.54 (dd, J = 12 Hz, J = 4 Hz, 1H); 2.38 (ddd, J = 12 Hz, J = 9 Hz, J = 4 Hz, 1H); 3.04 (dt, J = 9 Hz, J = 4 Hz, 1H); 3.53 (m, 1H); 3.74 (m, 1H); 6.53 (m, 2H); 6.90–7.46 (m, 10H)
	exo-**3d**			100° (ethanol)	$C_{21}H_{17}N$ (283.4)	2335	1.75 (dd, J = 12 Hz, J = 9 Hz, 1H); 2.06–2.45 (m, 2H); 3.46–3.80 (m, 2H); 6.20–6.70 (m, 2H); 7.00–7.50 (m, 10H)
2e	*endo*-**3e**	5/r.t./1 : 1.1	76 (4.5 : 1)[g]	80° (petrol ether)	$C_{27}H_{31}O_5P$ (466.5)	1740, 1240, 1170, 1060, 1030	0.87–1.30 (m, $3CH_3$); 2.10 (dd, J = 12 Hz, J = 10 Hz, 1H); 2.75 (ddd, J = 4 Hz, J = 12 Hz, J = 20 Hz, 1H); 3.33–4.18 (m, 8H); 6.18–6.33 (m, 1H); 6.38–6.52 (m, 1H); 7.00–7.45 (m, 10H)
	exo-**3e**			114° (petrol ether)	$C_{27}H_{31}O_5P$ (466.5)	1730, 1250, 1170, 1050, 1030	0.77 (t, J = 7 Hz, CH_3); 1.22 (dt, J = 2 Hz, J = 7 Hz, $2CH_3$); 1.93 (dd, J = 12 Hz, J = 18 Hz, 1H); 3.00 (ddd, J = 3 Hz, J = 12 Hz, J = 7 Hz, 1H); 3.45–4.25 (m, 8H); 6.30–6.55 (m, 2H); 6.90–7.40 (m, 10H)

Table. (Continued)

Dienophile	Product	Reaction conditions time [days]/temp. [°C]/ratio of **1** : **2**	Yield [%][a] (*endo*-/*exo*-)	m.p. [°C] (solvent)	Molecular Formula[b] or Lit. m.p. [°C]	I.R. (CCl_4)[c] ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS)[d] δ [ppm]
2f	*endo*-**3f**	5/r.t./1 : 5	62[h]	93° (methanol)	88°[2]	1700	1.74 (dd, J = 12 Hz, J = 4 Hz, 1H); 2.05 (ddd, J = 12 Hz, J = 9 Hz, J = 4 Hz, 1H); 3.18 (dt, J = 9 Hz, J = 4 Hz, 1H); 3.43 (m, 1H); 3.76 (m, 1H); 6.14 (dd, J = 6 Hz, J = 3 Hz, 1H); 6.40 (dd, J = 6 Hz, J = 3 Hz, 1H); 7.04–7.16 (m, 4H); 7.20–7.36 (m, 6H)
2g	*endo*-**3g**	2/0°/1 : 2	80[h]	oil	$C_{20}H_{17}NO_2$ (303.4)	1540, 1370	2.05 (dd, J = 13 Hz, J = 4 Hz, 1H); 2.43 (ddd, J = 13 Hz, J = 9 Hz, J = 4 Hz, 1H); 3.50 (m, 1H); 4.10 (m, 1H); 5.10 (dt, J = 9 Hz, J = 4 Hz, 1H); 6.18 (dd, J = 6 Hz, J = 3 Hz, 1H); 6.60 (dd, J = 6 Hz, J = 3 Hz, 1H); 6.90–7.50 (m, 10H)
2h	*endo*-**3h**	7/50°/1 : 2	10[h]	220° (cyclohexane/ethylacetate, 1 : 1)	$C_{26}H_{22}OS$ (382.5)	1045	1.08 (dd, J = 12 Hz, J = 4 Hz, 1H); 1.84 (ddd, J = 12 Hz, J = 8 Hz, J = 4 Hz, 1H); 3.58 (dt, J = 8 Hz, J = 4 Hz, 1H); 3.43 (m, 1H); 4.11 (m, 1H); 6.50–6.76 (m, 2H); 6.95–7.85 (m, 15H)
4	**5**	14[e]/r.t./1 : 1	82	92° (ether/petrol ether/ethanol, 10 : 10 : 1)	$C_{24}H_{24}N_2O_4$ (404.5)	1700	1.18 (t, J = 7 Hz, $2CH_3$); 4.10 (q, J = 7 Hz, $2CH_2$); 5.35 (m, 2H); 6.80 (m, 2H); 7.00–7.50 (m, 10H)

[a] Total yield of the isolated isomers.
[b] Satisfactory microanalyses obtained: C ±0.49, H ±0.33, Cl ±0.24, P ±0.34, S ±0.38.
[c] Measured on a Perkin Elmer 1310 spectrophotometer.
[d] Recorded on a Bruker AM 100 spectrometer.
[e] Reaction time is given in hours.
[f] The isomers could not be separated by simple column chromatography, their ratio results from the ^{1}H-N.M.R. spectra.
[g] The isomers were separated by column chromatography on silica gel (cyclohexane/ethyl acetate, 5 : 1); R_f for *endo*-**3e** = 0.34, R_f for *exo*-**3e** = 0.20.
[h] Only *endo*-isomer was obtained.

The mixture is stirred at room temperature for 3 h, diluted with water (800 ml) and extracted with dichloromethane (3 × 200 ml). Evaporation of the solvent and recrystallization from diisopropyl ether affords **7**; yield: 13.7 g (91%); m.p. 93°C.

$C_{20}H_{18}O$ (274.3) calc. C 87.57 H 6.60
found 87.40 6.60

I.R. (CCl_4): ν = 1760 cm^{-1} (C=O).

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.50–2.20 (m, 4H); 2.15 (d, 1H, J = 18 Hz); 2.52 (q, 1H, J = 18 Hz, J = 4 Hz); 3.20 (m, 2H); 7.00–7.50 ppm (m, 10H).

This work is dedicated to Prof. Rolf Sammet on the occasion of his 65th birthday.

Received: January 15, 1985

[1] Yates, P. *Adv. Alicyclic Chem.* **1968**, *2*, 59.
[2] Alder, K., Rühmann, R. *Liebigs Ann. Chem.* **1949**, *566*, 1. Alder, K., Chambers, F.W., Trimborn, W. *Liebigs Ann. Chem.* **1949**, *566*, 27.
[3] Recently this method has been used for the protection of double bonds:
(a) Ichihara, A., Kimura, R., Oda, K., Sakamura, S. *Tetrahedron Lett.* **1976**, 4741.
(b) Kimura, R., Ichihara, A., Sakamura, S. *Synthesis* **1979**, 516.
(c) Ichihara, A., Kimura, R., Yamada, S., Sakamura, S. *J. Am. Chem. Soc.* **1980**, *102*, 6353.
[4] Uebersax, B., Neuenschwander, M., Kellerhals, H.P. *Helv. Chim. Acta* **1982**, *65*, 74.
[5] Houk, K.N., George, J.K., Duke, R.E. *Tetrahedron* **1974**, *30*, 523.
[6] Ranganathan, S., Ranganathan, D., Mehrotra, A.K. *Synthesis* **1977**, 289.
[7] Paquette, L.A., Moerck, R.E., Harirchian, B., Magnus, P.D. *J. Am. Chem. Soc.* **1978**, *100*, 1597.
[8] Weinreb, S.M., Staib, R.R. *Tetrahedron* **1982**, *38*, 3087.
[9] Vieira, E., Vogel, P. *Helv. Chim. Acta* **1982**, *65*, 1700.
[10] In principle the *exo*/*endo*-mixture of **3c** can be employed, cf.: Ref.[6].
[11] Freeman, P.K., Balls, D.M., Brown, D.J. *J. Org. Chem.* **1968**, *33*, 2211.